

TABLE 3-12. LUNG CANCER RISKS, BY DOSE, AMONG SOUTH CAROLINA ASBESTOS TEXTILE WORKERS (McDonald et al., 1983a)

Exposure in mppcf-y ^a	SMR	RR ^b
5 (<10)	143.1 (31) ^c	1.00 (25)
15 (10-19)	182.7 (5)	0.98 (3)
30 (20-39)	304.2 (8)	2.95 (8)
60 (40-79)	419.5 (7)	4.32 (7)
120 (>80)	1031.9 (8)	15.00 (6)

Complete cohort: 199.5 (53)

Estimated average cumulative exposure: 10.3 mppcf-y.

^aExposure accumulated to 10 years before death.

^bRelative risk from an internal case-control analysis.

^c() = number of deaths.

Regression equations

$$\text{SMR} = 110 + 6.22(\pm 0.76) \times \text{mppcf-y weighted}$$

$$\text{SMR} = 63 + 7.68(\pm 0.76) \times \text{mppcf-y unweighted}$$

$$\text{RR} = 0.61 + 0.068(\pm 0.019) \times \text{mppcf-y weighted}$$

$$\text{RR} = -0.80 + 0.123(\pm 0.017) \times \text{mppcf-y unweighted}$$

Weighted regression equation forced through an SMR of 100:

$$\text{SMR} = 100 + 6.63 (\pm 0.61) \times \text{mppcf-y}$$

value of $K_L = 0.037$. We will use 0.025, the average of 0.014 and 0.037, to represent this study. The agreement with the results of Dement et al. (1982, 1983a,b) is very good.

3.9.3 Textile Products Manufacturing, Rochdale, England (Chrysotile); Peto (1980)

Table 3-13 shows the lung cancer and mesothelioma mortality experience from an often-studied British textile plant (Doll, 1955; British Occupational Hygiene Society, 1968; Berry et al., 1979; Knox et al., 1968; Peto, 1980; British Occupational Hygiene Society, 1983). The data are difficult to interpret because dust concentrations have changed fairly dramatically over the past five decades of plant operations, and so have subsequent estimates of

TABLE 3-13. MORTALITY EXPERIENCE OF 679 MALE ASBESTOS TEXTILE WORKERS
(Peto, 1980)

Year first exposed	Period since first exposure (yrs)	Man-years	Lung cancer		Mesothelioma	
			O	E	O	rate per 10 ³ p-y
1933-1950 N = 424	10-14	1633	2	1.80	0	0.0
	15-19	1860	4	2.98	0	0.0
	20-24	1760	3	3.97	1	0.6
	25-29	1496	10	4.54	2	1.3
	30-34	837	8	3.14	2	2.4
	35-39	507	1	2.20	2	3.9
	Total	8093	28	18.63	7	-
1951 or later N = 255	10-14	1123	1	1.30	0	0.0
	15-19	1022	3	1.74	0	0.0
	20-24	556	7	1.31	0	0.0
	25-29	96	1	0.31	0	0.0
	Total	2797	12	4.65	0	-

those concentrations. No measurements of dust concentrations were made prior to 1951. Between 1951 and 1964, thermal precipitators were used to evaluate total dust levels; thereafter, filter techniques similar, but not identical, to those in the United States were used. Average fiber concentrations are published for earlier years based on a comparison of fiber counting with thermal precipitator techniques (Berry, 1973). Later these estimates were stated to be inaccurate; Berry et al. (1979) reported that a re-evaluation of the work histories indicated that some men had spent more time in less dusty jobs than previously believed and that previous average cumulative doses to 1966 had been overestimated by 50 percent.

Recently, as part of the British Government's review of its asbestos standard, the hygiene officers of the plant re-evaluated previously reported exposure data. It is now suggested that earlier static sampling methods underestimated personal exposures by a factor of about 2, and that whole field, rather than graticule field, microscopic counting understated fiber concentrations by another factor of 2 to 2.5 (Steel, 1979). In 1983, the

British Occupational Hygiene Society (1983) reported information on the differences between personal and static sampling. Data were presented for thirty-one simultaneous samples comparing the two techniques, the personal samplers indicating a greater fiber concentration in 22 cases. Using these data, the BOHS committee evaluated the cumulative fiber exposure (as of approximately 1976) for 284 individuals employed for 10 or more years subsequent to 1951. The overall average of the entire group was 182 f-y/ml. This is slightly less than the estimate of Peto (1980), who suggested that the exposure of 10+ years employees was 200-300 f-y/ml. However, Peto's estimate was based on preliminary data on only 126 men first employed between 1951 and 1955 (see Table 3-14).

These most recent estimates are clouded by questions concerning the appropriateness of multiplying static sampler concentrations by a factor approaching two. The BOHS data are directly contradicted by published data (See Table 3-15) from the factory on other comparisons of static and personal sampling results by job (Smither and Lewinsohn, 1973). Dr. Lewinsohn (1983) confirmed these results. He stated that the static sampler concentrations were generally higher than those of the personal samplers of men working at the monitored job. The company placed the static samplers to best reflect the breathing zone dust concentrations of machine operators while tending machines. Dr. Lewinsohn (1983) stated that if a machine were running smoothly, a worker would move away to the aisle adjacent to the machine from where he or she could continue to observe the operation and experience a lower dust concentration. The difference between static and personal sampling data appears to be greater in the dustier jobs. In the Rochdale factory, the average of the ratios of static to personal sample concentrations at the same work station is 1.8 (1.5 if the fiberizing operation is not considered). The recent comparison may not reflect the movement of a worker from his machine.

We will use a value of 200 f-y/ml to represent cumulative exposure of the post-1951 group fifteen or more years from onset of exposure, which probably overestimates the effective exposure of the group. While 200 f-y/ml, the average dose of all men employed 10 or more years, may underestimate the average total dose of men employed 15 or more years, it certainly overestimates the effective dose that accumulates to about 10 years prior to end of follow-up or death. As was shown above, this yields a K_L of 0.011. To reflect what could be a twofold lesser exposure, the upper exposure-related uncertainty in risk was increased from 2 to 4 in Figure 3-7.

TABLE 3-14. PREVIOUS AND REVISED ESTIMATES OF MEAN DUST LEVELS IN f/m³
(WEIGHTED BY THE NUMBER OF WORKERS AT EACH LEVEL IN SELECTED YEARS)

	1936	1941	1946	1951	1956	1961	1966	1977	1974
Previous estimates corresponding to early fiber counts	13.3	14.5	13.2	10.8	5.3	5.2	5.4	3.4	-
Revised estimates corresponding to modern counting of static samples ^a	No measurements prior to 1951			32.4	23.9	12.2	12.7	4.7	1.1

^aThese estimates are based on preliminary data on 126 workers first employed between 1951 and 1955, and should be regarded as provisional.

Source: Peto (1980).

TABLE 3-15. DUST LEVELS: ROCHDALE ASBESTOS TEXTILE FACTORY, 1971

Department	Process	Static	Personal
Fiberizing	Bag slitting	3	1
	Mechanical bagging	4	1
Carding	Fine cards	3.5	2
	Medium cards	4.5	3.5
	Coarse cards	8	6
	Electrical sliver cards	1.5	1
Spinning	Fine spinning	2.5	3
	Roving frames	6	3
	Intermediate frames	5.5	3
Weaving	Beaming	0.5	0.5
	Pirn weaving	1.5	1
	Cloth weaving	2	1
	Listing weaving	0.5	0.5
Plaiting	Medium plaiting	4	2

Source: Smither and Lewinsohn (1973).

A second difficulty of the British textile factory study is that the dose-response data calculated from groups exposed before and after 1950 differ considerably. While no cumulative exposure data are published for the pre-1951 group, it is surprising that more disease is seen in the latter group, as the average intensity of exposure was certainly greater for the earlier group, perhaps by a factor of three. It is difficult to reconcile the differences between the two subcohorts employed in this facility. The data are severely limited by the relatively small size of the cohort and the few deaths available for analysis. Nevertheless, what would appear to be a nearly tenfold difference in the estimated risk of death from lung cancer suggests the possible existence of some unidentified bias in the pre-1951 group. The post-1950 group's mortality experience is more in accord with U.S. textile plants. The finding of only a 50 percent increase in lung cancer in exposure circumstances leading to 5.3 percent of deaths being from asbestosis is certainly unusual, as is the finding that there are as many mesotheliomas as excess lung cancers.

Doll and Peto (1985) recently reviewed the new information on the health effects of asbestos for the British Health and Safety Commission. Many of the above uncertainties, particularly that of the ratio of personal to static sampling counts, are discussed. A regression analysis of the ratio of personal to static counts against mean concentration indicated that the ratio is greater than one for concentrations less than 2 f/ml, but less than one for higher concentrations. Doll and Peto (1985) estimate values of K_L from the mortality in an expanded and updated study of the Rochdale cohort. Their results indicate K_L is 0.015 for workers first employed after 1950 and 0.0054 for all workers first employed after 1932.

3.9.4 Textile and Friction Products Manufacturing, United States (Chrysotile, Amosite, and Crocidolite); McDonald et al. (1983b); Robinson et al. (1979)

A plant located near Lancaster, Pennsylvania, which produced mainly textiles but also friction products and packings, was studied by Robinson et al. (1979), McDonald et al. (1983b), and earlier by Mancuso and Coulter (1963) and Mancuso and El-attar (1967). The plant, which began operations in the early 1900s, used between 3000 and 6000 tons of chrysotile per year over most of the period of its operation. Amosite constituted less than 1 percent of the fiber used, except for a three-year period, 1942 - 1944, when 375-600 tons of amosite were used in insulation blankets and mattresses. Crocidolite usage was approximately 3-5 tons per year (Robinson et al., 1979). The reports of

Robinson et al. (1979), Mancuso and Coulter (1963), and Mancuso and El-attar (1967) provide no information on the exposure of the cohort members to asbestos; so they cannot be used in establishing exposure-response relationships. In the study of McDonald et al. (1983b), dust concentrations, measured in mppcf, available from the 1930s through 1970 were used. However, no attempt was made to relate particle exposures to fiber exposures. The study cohort of McDonald et al. (1983b) comprised all individuals employed for one or more months prior to January 1, 1959 with their Social Security file identifiable in the Social Security Administration offices. These individuals were traced through December 31, 1977, and cause-specific mortality ratios, based on state rates, were related to cumulative dust exposure.

The results for lung cancer are shown in Table 3-16. The regression of SMR on dose has an unusually low intercept of 53. The overall SMR for lung cancer is also low. The low local rates (30.1 versus 37.7 for the state) (Mason and McKay, 1974) do not fully account for these deficits. Smoking histories are reported for only 36 individuals and indicate no unusual pattern. Because the full deficit cannot be explained, we have adjusted the slope by the ratio of the local to state lung cancer rates (0.81) rather than by 0.53, resulting in a slope of 0.032. The adjusted slope of the RR regression is 0.051. If these two values are averaged and a factor of 3 is used to convert from mppcf to f/ml, the exposure-response relationships give average $K_L = 0.014$. The factor of 3 was previously measured in textile manufacturing, the predominant activity in this plant. Calculating K_L using the overall SMR of the study suggests that the lower confidence limit of K_L is 0, but the SMR and RR regression lines strongly contradict this. Thus, for the lower confidence limit we will use a value calculated from the highest exposure relationship, where the uncertainty in comparison rates has less of an effect.

3.9.5 Friction Products Manufacturing, Great Britain (Chrysotile and Crocidolite); Berry and Newhouse (1983)

Berry and Newhouse analyzed the mortality of a large workforce manufacturing friction products. All individuals employed in 1941 or later were included in the study, and the mortality experience through 1979 was determined. Exposure estimates were made by reconstructing the work and ventilation conditions of earlier years. Fiber measurements from these reconstructed conditions suggested that exposures prior to 1931 exceeded 20 f/ml but those afterwards seldom exceeded 5 f/ml. From 1970, exposures were less than 1 f/ml.

TABLE 3-16. LUNG CANCER RISKS, BY DOSE, AMONG PENNSYLVANIA ASBESTOS
TEXTILE AND FRICTION PRODUCTS WORKERS
(McDonald et al., 1983b)

Exposure in mppcf-y ^a	SMR	RR ^b
5 (<10)	66.9 (21) ^c	1.00 (20)
15 (10-19)	83.6 (5)	0.83 (4)
30 (20-39)	156.0 (10)	1.54 (10)
60 (40-79)	160.0 (6)	2.90 (6)
120 (>80)	416.1 (11)	6.82 (11)

Complete cohort: 105.0 (53)

Estimated average cumulative exposure: 16.9 mppcf-y.

^aExposure accumulated to 10 years before death.

^bRelative risk from an internal case-control analysis.

^c() = number of deaths.

Regression equations

$$\begin{aligned} \text{SMR} &= 53 + 2.58(\pm 0.45) \times \text{mppcf-y} && \text{weighted} \\ \text{SMR} &= 41 + 2.94(\pm 0.42) \times \text{mppcf-y} && \text{unweighted} \end{aligned}$$

$$\begin{aligned} \text{RR} &= 0.70 + 0.036(\pm 0.010) \times \text{mppcf-y} && \text{weighted} \\ \text{RR} &= 0.24 + 0.050(\pm 0.005) \times \text{mppcf-y} && \text{unweighted} \end{aligned}$$

Weighted regression equation forced through an SMR of 100:

$$\text{SMR} = 100 + 1.22 (\pm 1.07) \times \text{mppcf-y}$$

These relatively low intensities of exposure kept the average cumulative exposure for the group to less than 40 f-y/ml.

The overall mortality of all study participants, 10 years and more after onset of exposure, was no greater than expected for all causes. Data for lung cancer are shown in Table 3-17. Cancer of the lung and pleura was slightly elevated in men (151 observed versus 139.5), but the excess was largely accounted for by eight mesothelioma deaths. No unusual mortality was found in those employed 10 or more years. Using a case-control analysis according to cumulative exposure, Berry and Newhouse (1983) estimated that the lung cancer increased risk was 0.06 percent per f-y/ml ($K_L = 0.00058$), with an upper 90 percent confidence limit of 0.8 percent per f-y/ml. Table 3-17 lists the results of the case control analysis. The weighted regression of RR on dose

has a negative slope. The ratio of excess lung cancer to average group exposure yields a value of $K_L = 0.00068 = [(143/139.5)-1]/37.1$. We will use the value published by Berry and Newhouse, 0.00058, and their confidence limits for K_L .

TABLE 3-17. LUNG CANCER RISKS, BY DOSE, AMONG BRITISH ASBESTOS FRICTION PRODUCTS WORKERS (Berry and Newhouse, 1983)

Exposure in mppcf-y	RR ^a
5 (0-9)	1.00 (50) ^b
30 (10-49)	0.79 (37)
75 (50-99)	0.86 (13)
200 (100-356)	0.88 (5)

Estimated average cumulative exposure: 31.7 f-y/ml.

^aRelative risk from an internal case-control analysis.

^b() = number of deaths.

Regression equations

$$RR = 0.91 - 0.00076(\pm 0.0016) \times f\text{-y/ml weighted}$$

$$RR = 0.90 - 0.00019(\pm 0.00070) \times f\text{-y/ml unweighted}$$

3.9.6 Friction Products Manufacturing, United States (Chrysotile); McDonald et al. (1984)

McDonald et al. (1984) analyzed the mortality of the workforce employed in friction products production in the United States and attempted to relate it to cumulative dust exposure. However, a highly unusual mortality experience is observed. The overall mortality shows an elevated risk of death in the complete cohort for virtually all causes, largely confined to individuals employed for less than one year. The correlation of respiratory cancer SMR with cumulative dust exposure of those employed for more than one year shows little, if any, trend with increasing dust exposure, even though the overall SMR for lung cancer (see Table 3-18) is 137 for these individuals. The slopes of the regression equations of SMR on dose are slightly negative and those of relative risk are slightly positive. As with the McDonald et al. (1983b) Pennsylvania textile study, we will use the dose-response regression relationship for the measure of risk and set $K_L = 0.0001$ for this group. In Figure 3-7, this represents "zero" for the purpose of calculating geometric means.

TABLE 3-18. LUNG CANCER RISKS, BY DOSE, AMONG ASBESTOS
FRICTION PRODUCTS PRODUCTION WORKERS
(McDonald et al., 1984)

Exposure in mppcf-y	SMR	RR ^a
5 (<10)	167.4 (55) ^b	1.00 (54)
15 (10-19)	101.7 (6)	0.40 (4)
30 (20-39)	105.4 (5)	0.91 (5)
60 (40-79)	162.8 (6)	1.40 (16)
120 (>80)	55.2 (1)	1.13 (1)

Complete cohort: 148.7 (73)

1+ yrs employment: 136.8 (49)

Estimated average cumulative exposure: 10.3 mppcf-y.

Estimated average exposure for
those employed more than 1 year: 15.5 mppcf-y.

^aRelative risk from an internal case-control analysis.

^b() = number of deaths.

Regression equations

$$\text{SMR} = 160 - 0.85(\pm 0.52) \times \text{mppcf-y} \quad \text{weighted}$$

$$\text{SMR} = 147 - 0.62(\pm 0.46) \times \text{mppcf-y} \quad \text{unweighted}$$

$$\text{RR} = 0.69 + 0.00006(\pm 0.01) \times \text{mppcf-y} \quad \text{weighted}$$

$$\text{RR} = 0.78 + 0.0041(\pm 0.0039) \times \text{mppcf-y} \quad \text{unweighted}$$

Weighted regression equation forced through an SMR of 100:

$$\text{SMR} = 100 + 0.13 (\pm 0.83) \times \text{mppcf-y}$$

The low value, however, is qualified by the overall high lung cancer mortality. As the origin of this elevated lung cancer mortality is workers employed for more than one year (where total mortality is close to that expected) is unknown, the upper limit of uncertainty will be given by the upper confidence limit on the ratio of lung cancer excess risk to average exposure in the 10-19 mppcf-y exposure groups. This procedure is similar to that used to estimate the lower confidence limit in the Pennsylvania textile cohort.

3.9.7 Mining and Milling, Quebec, Canada (Chrysotile); Liddell et al. (1977); McDonald et al. (1980)

The results reported by Liddell et al. (1977) and McDonald et al. (1980) on mortality (Table 3-19) according to total dust exposure in Canadian mines and mills can be converted to relationships expressed in terms of fiber exposures. SMR values are provided by McDonald et al. (1980) for various exposure categories in four different duration-of-employment categories. A weighted regression analysis of these data yields a relationship, $SMR = 92 + 0.13 \times mppcf\text{-}y$. Using a value of 3 f/ml/mppcf for the particle fiber conversion factor yields a K_L of 0.00043. The factor of 3 f/ml/mppcf is the midpoint of the range of 1-5 f/ml/mppcf suggested by McDonald et al. as being applicable to most jobs in mining and milling. However, since McDonald et al. used the rates of the Province of Quebec for their comparison data, K_L is likely to be underestimated. In an earlier paper, McDonald et al. (1971) suggested that the lung cancer rates in the counties adjacent to the asbestos mining counties were about two-thirds those of the Province. This is substantiated by lung cancer incidence rates, in the Province of Quebec, published by Graham et al. (1977). These data for the years 1969-1973 are shown in Table 3-20 and confirm the earlier statement of McDonald et al. (1971). Thus, the above K_L will be multiplied by a factor of 1.5. Liddell et al. (1977) performed a case control analysis of the relative risk of lung cancer in this same period. Their regression equation suggests a K_L of 0.00057. We will use the average of these two estimates, 0.00060, for K_L .

The overall SMR of 125 based upon Quebec rates, for lung cancer mortality among all miners is surprising. In studies of the mortality of male residents of Thetford, in the midst of the Canadian asbestos mining area (Toft et al., 1981; Wigle, 1977), an SMR of 184 was seen for lung cancer and 230 for cancer of the stomach. Because no corresponding increases were seen in female cancer rates, Toft et al. (1981) and Wigle (1977) attributed the excesses to occupational exposure in the mines. Siemiatycki (1982) presented data on the mortality of male residents of Asbestos and Thetford Mines, Quebec, that indicated an SMR for lung cancer of 148 compared to Quebec rates. The origin of a lower SMR for those employed in mining and milling compared to all male residents could result from the departure of most short-term workers from the area, but data on this possibility are lacking. While the risk appears low compared to town mortality, the agreement between the SMR and RR analyses is very good.

TABLE 3-19. LUNG CANCER RISKS, BY DOSE, AMONG
CANADIAN CHRYSOTILE ASBESTOS MINERS

McDonald et al., 1980 in mppcf-y	SMR	Liddell et al., 1977 Exposure in mppcf-y	RR ^a
<u>< 1 year of employment</u>			
.5	117 (19) ^b	3 (<6)	1.00 (43)
1.7	91 (12)	8 (6-10)	1.07 (10)
5.8	88 (9)	20 (10-30)	0.96 (24)
39.0	80 (7)	65 (30-100)	1.16 (37)
		200 (100-300)	1.22 (31)
<u>1 to 4.9 years of employment</u>			
		450 (300-600)	1.88 (27)
3.3	66 (5)	800 (600-1000)	2.39 (18)
13.6	95 (13)	1250 (1000-1500)	3.49 (10)
59.0	82 (6)	1750 (1500-2000)	4.97 (6)
231.3	78 (5)	3000 (2000+)	5.42 (9)
<u>5 to 19.9 years of employment</u>			
16.0	141 (13)		
58.2	122 (14)		
178.5	83 (7)		
704.0	217 (16)		
<u>20+ years of employment</u>			
104.6	121 (28)		
261.3	108 (20)		
549.1	220 (24)		
1141.4	265 (32)		

Complete cohort:

125 (230)

Estimated average cumulative exposure: 185 mppcf-y.

^aRelative risk from an internal case-control analysis.^b() = number of deaths.

Regression equations

$$\text{SMR} = 92 + 0.13(\pm 0.024) \times \text{mppcf-y} \quad \text{weighted}$$

$$\text{SMR} = 93 + 0.13(\pm 0.024) \times \text{mppcf-y} \quad \text{unweighted}$$

$$\text{RR} = 0.99 + 0.0017(\pm 0.00013) \times \text{mppcf-y} \quad \text{weighted}$$

$$\text{RR} = 1.10 + 0.0017(\pm 0.00013) \times \text{mppcf-y} \quad \text{unweighted}$$

Weighted regression equation forced through an SMR of 100:

$$\text{SMR} = 100 + 0.12 (\pm 0.02) \times \text{mppcf-y}$$

TABLE 3-20. LUNG CANCER INCIDENCE RATES IN URBAN AND
RURAL AREAS OF QUEBEC PROVINCE,
1969-1973

Region	MALES		FEMALES	
	Rate	Population	Rate	Population
Asbestos counties	33.59	57,685	4.39	57,630
Peripheral counties	23.71	209,320	4.64	210,180
Other rural	27.29	1,295,895	3.87	1,264,795
Montreal	48.67	1,222,245	8.70	1,281,855
Quebec City	50.53	204,435	6.96	218,745
Province	37.47	2,989,580	6.20	3,033,215
Ratio: Rural/Province	.728		.624	
Ratio: Peripheral/Province	.633		.748	

From: Graham et al. (1977).

3.9.8 Mining and Milling, Thetford Mines, Canada (Chrysotile); Nicholson (1976b); Nicholson et al. (1979)

Somewhat higher risks in the mining industry were obtained by Nicholson (1976b) and Nicholson et al. (1979) from the mortality experience of a smaller group of miners and millers employed 20 or more years at Thetford Mines, Quebec. In this study, 178 deaths occurred among 544 men who were employed during 1961 in 1 of 4 mining companies. In the ensuing 16 years of follow-up, 26 deaths occurred from asbestosis, 28 (25 on DC) from lung cancer (11.1 expected), and 1 from mesothelioma.

Fiber measurements were made during 1974 in five mines and mills, and data on particle counts from 1948 were supplied by the Canadian Government. From these data, exposure estimates were made for each of the 544 individuals according to their job histories. Fiber exposures for earlier years were estimated by adjusting current measurements by changes in particle counts observed since 1950. The 20-year cumulative exposure for the entire group was estimated to be 1080 f-y/ml.

The mortality experience of the whole group from an earlier follow-up was reported by two exposure categories (Nicholson, 1976b) (see Table 3-21). The difference in lung cancer SMRs in these two exposure groups suggests that $K_L = 0.0023 [(333-55)/(1760-560)/100]$. However, Canada rates were used to estimate expected deaths and these overestimated mortality. As with the McDonald

TABLE 3-21. EXPECTED AND OBSERVED MORTALITY AMONG 544 QUEBEC ASBESTOS MINE AND MILL EMPLOYEES, 1961-1973

Causes of death	Average Exposure 560 f-y/m ^a			Cumulative Exposure 1760 f-y/m ^a		
	Exp.	Obs.	Ratio	Exp.	Obs.	Ratio
All causes of death	68.29	65	0.95	44.56	67	1.50
All cancers	15.45	15	0.97	10.11	18	1.78
Lung	4.52	7	1.55	3.00	13	4.33
Mesothelioma	--	1	--	--	0	--
Gastrointestinal	4.18	3	0.72	2.71	3	1.11
Other cancers	6.75	4	0.59	4.40	2	0.45
Respiratory diseases	4.79	10	2.09	3.02	15	4.24
Pneumonia	2.01	1	0.50	1.27	1	0.78
Asbestosis	--	7	--	--	11	--
Other respiratory	2.79	2	0.72	1.76	3	1.70
All other causes	48.05	40	0.83	31.43	34	1.08

^aBest estimate cause of death.

et al. (1980) study, K_L will be multiplied by a factor of 1.5 to 0.0034 and then reduced to 0.0030 to convert to DC lung cancer diagnosis. An analysis, adjusted to local rates, using the overall SMR and average group exposure, yields a value of $K_L = 0.0017$. Because there is likely to be greater uncertainty associated with the regression analysis than with the use of average values, we will use the estimate of $K_L = 0.0017$ for this study.

3.9.9 Mining and Milling, Italy (Chrysotile); Rubino et al. (1979)

A final study of chrysotile mining and milling is that of Rubino et al. (1979) of the Balangero Mine and Mill, northwest of Turin. A cohort was established of 952 workers, each with at least 30 calendar days of employment between January 1, 1930 and December 31, 1965, who were alive on January 1, 1946. Ninety-eight percent of the cohort was traced and their mortality experience through 1975 was ascertained. Overall, an exceptionally high mortality was seen compared to that expected; 332 deaths were observed versus 214.4 expected. The excess mortality, however, was largely confined to non-malignant respiratory diseases, cardiovascular diseases, and accidents. The overall SMR for all malignant neoplasms was 106, with only cancer of the

larynx found to be significantly in excess in the whole group. While the overall data were relatively unremarkable, the age standardized rates of lung cancer according to cumulative dust exposure showed a relative risk of 2.29 (2.54 based upon cancer of the lung and pleura) for a high exposure group (376 f-y/ml) compared to a low exposure group (75 f-y/ml) [$K_L = 1.29/(376-75) = 0.0043$]. A case-control analysis of lung cancer according to cumulative dust exposure showed a relative risk of 2.61. Adjusting to a relative risk of 1 at zero exposure gives a K_L of 0.089. However, the characterization of the exposures in the study may have created an artificially steeper dose-response relationship than actually exists. Rubino et al. (1979) calculated the person-years at risk in two exposure categories (± 100 f-y/ml). A person contributed to the lower category until his exposure exceeded 100 f-y/ml. However, in Section 3.6 it is shown that there is a 5-10 year lag before the risk is manifest from a given exposure. Thus, the transition should be delayed by 5-10 years after achievement of 100 f-y/ml. Deaths and person-years at risk occurring in this delay period should be attributed to the lower exposure category. If lung cancer deaths occurred in the delay period, the dose-response relationship is probably artificially steeper than it should be; if no lung cancer deaths occurred, it is artificially shallower. The overall SMR of those 20 years from onset yields a K_L of 0.00013 $[(103.4 - 100)/100/273 \text{ f-y/ml}]$. The uncertainty in the estimate of K_L is enormous. We will use the geometric mean of 0.0043 and 0.00013, 0.00075, to represent K_L .

3.9.10 Insulation Manufacturing, Paterson, NJ (Amosite); Seidman et al. (1979)

The study by Seidman et al. (1979) also can be used for quantitative risk estimates: The study was recently updated and the new mortality results were submitted for the OSHA hearings record on a revised standard for asbestos (Seidman, 1984). In this update, dose-response data, based upon estimates of individual exposures for each cohort number, are available. Data for lung cancer are listed in Table 3-22.

Because no data exist on air concentrations for the Paterson factory, the data in terms of fiber counts were estimated from air concentrations in two other plants manufacturing the same products with the same fiber and machinery. One of these plants, in Tyler, Texas, opened in 1954 and operated until 1971; the other, in Port Allegany, Pennsylvania, opened in 1964 and closed in 1972. As in the Paterson factory, efforts to control dust in these newer plants were

TABLE 3-22. CUMULATIVE OBSERVED AND EXPECTED DEATHS FROM LUNG CANCER
5 TO 40 ELAPSED YEARS SINCE ONSET OF WORK IN AN AMOSITE ASBESTOS FACTORY,
1941-1945, BY ESTIMATED FIBER EXPOSURE
(Seidman, 1984)

Cumulative exposure (f-y/ml)	Number of men	Number of deaths (BE)	Number of deaths (DC)	Expected deaths ^a	SMR (BE)	SMR (DC)
<6.0	177	15	14	5.31	282	264
6.0 - 11.9	109	12	12	2.89	415	415
12.0 - 24.9	139	15	15	3.39	442	442
25.0 - 49.9	123	13	12	2.78	468	432
50.0 - 99.9	104	17	17	2.38	714	714
100.0 - 149.9	57	9	9	1.49	604	604
150.0 - 249.9	58	15	12	1.32	1136	909
250+	53	15	11	0.94	1596	1170
Total	820	111	102	20.51	541	497

Estimated average cumulative exposure: 67.1 f-y/ml.

BE = best estimate of cause of death based on all medical evidence.

DC = Death certificate cause of death.

^aExpected deaths based on New Jersey white male quinquennial age and calendar year period specific death rates.

Regression equations

$$\begin{aligned} \text{SMR} &= 325 + 2.72(\pm 0.54) \times \text{f-y/ml} \quad \text{weighted} \\ \text{SMR} &= 330 + 2.45(\pm 0.37) \times \text{f-y/ml} \quad \text{unweighted} \end{aligned}$$

Weighted regression equation forced through an SMR of 100:

$$\text{SMR} = 100 + 4.28 (\pm 1.17) \times \text{f-y/ml}$$

limited. One, in fact, was housed in a low Quonset-type building where the confined space exacerbated dust conditions. During 1967, 1970, and 1971, asbestos fiber concentrations in these plants were measured by the U.S. Public Health Service and the results published in the Asbestos Criteria Document of the National Institute for Occupational Safety and Health (1972). These data were supplemented by company data in one plant and individual worker estimates of dustiness (which were used for some jobs not sampled).

The zero dose SMR intercept of 325 is highly anomalous and difficult to understand. The use of New Jersey rates for calculating expected deaths is

appropriate for the Paterson area (the age standardized county rates are 46.8 versus 46.3 for the state). The high intercept is largely the result of a disproportionately high risk observed in individuals employed for less than 6 months, whose SMR is 295 (32 observed, 10.86 exposed). Certainly, new employees usually get the dustiest jobs and if there are effects of intensity of exposure separate from those of dose, very dusty environments may have contributed a disproportionately greater risk. However, longer term employees also would have had such jobs at one time and intensity effects are not seen in other asbestos-exposed groups. Another possibility is that the short-term group includes many men exposed to carcinogens at work elsewhere or they are unusually heavy smokers. Abnormally high risks were also seen in the short-term employees of a friction products plant studied by McDonald et al. (1984). A third possibility is that there could have been misestimates of exposure for the short-term employees who would have the extremely dusty jobs. However, the dose-response relationship for death from asbestos is a reasonable one and there is no unusual mesothelioma risk among those employed less than 6 months. Finally, part of the excess may simply be the result of statistical fluctuations.

The values of K_L estimated by different treatments of the data range from 0.0084, obtained by adjusting the slope of the weighted regression line by the intercept (2.72/325), to 0.059, obtained by dividing the excess overall lung cancer SMR by the average group exposure $[(495-100)/67.1/100]$. If inappropriate underlying rates (because of other exposures) apply only to the short-term group, an adjustment can be made by forcing the dose-response line through the origin. This yields a value of $K_L = 0.043$. Because this is most likely to be the case, this value will be used for K_L .

The uncertainty in the value extends from 0.0084 to 0.074 to account for the statistical variability on the number of deaths and different values of K_L obtained from different analysis procedures.

3.9.11 Insulation Application, United States (Chrysotile and Amosite)

The previously discussed mortality study of Selikoff et al. (1979) can be combined with published information on asbestos exposures measured for members of this cohort to obtain an exposure-risk estimate. The data on insulation workers' exposure were reviewed by Nicholson (1976a) and are summarized in Table 3-23. Using the standard membrane filter technique of the U.S. Public Health Service for counting asbestos fibers (Leidel et al., 1979), three

TABLE 3-23. SUMMARY OF AVERAGE ASBESTOS AIR CONCENTRATION
DURING INSULATION WORK^a
(Selikoff et al., 1979)

Research group	Average fiber concentration, f/ml	
	Light and heavy construction	Marine work
Nicholson (1975)	6.3	
Cooper and Balzer (1973)	2.7	6.6
Ferris et al. (1971)		2.9
Harries (1971)		8.9
Average concentrations of all visible fibers counted with a konimeter and bright-field microscope.		
Murphy et al. (1971)		8.0
Fleischer et al. (1946)		30-40
Estimates of past exposure based on current membrane-filter data.		
Nicholson (1976a)	10-15	

^aAverage concentrations of fibers longer than 5 μ m evaluated by membrane filter techniques and phase-contrast microscopy.

Source: Nicholson (1976a).

different laboratories in the United States found that the average fiber concentration of asbestos dust in insulation work, between 1968 and 1971, ranged from about 3 to 6 f/ml. A similar study in the Devonport Naval Dockyard in Great Britain, with the same techniques, obtained 8.9 f/ml for the average of long-term sampling of asbestos concentrations measured during application of insulating materials aboard ship (Harries, 1971). In the research that led to these data, it was reported that peak exposures could be extremely high. It was not uncommon, for example, to get 2- to 5-minute concentrations of asbestos exceeding 100 f/ml during the mixing of cement. This mixing, however, would only be done perhaps once an hour, so that exposures measured during that hour, including the mixing, would seldom average more than 10 f/ml. Similar experiences were subsequently reported by Cooper and Miedema (1973), who stated, "Peak concentrations may be high for brief periods, while time-weighted averages are often deceptively low."

Direct information on asbestos fiber concentration measured by the currently prescribed analysis procedures, has been available only since 1966. Although insulation materials have changed from earlier years (fiber glass has found extensive use, and work with cork is seldom done today) and changes in the asbestos composition of insulating products have taken place (pipe coverings and insulation blocks may have had twice the asbestos content in earlier years), work practices are virtually identical and few controls of consequence were in use. Therefore, dust concentrations measured under these conditions have relevance for estimating the levels of past years. Considering the possible doubling of the asbestos content of older insulation materials, the data from the studies listed in Table 3-23 suggest that the average exposures of insulation workers in the United States during past years could have ranged from 10-15 f/ml for commercial and industrial construction. In marine construction, it may have been between 15 and 20 f/ml. We will use a value of 15 f/ml as an overall average. Because of the great variability in work activities of this group, the range of uncertainty in the exposure is estimated to be from 7.5 to 45 f/ml, and this range is indicated in Figure 3-7.

This information and the data in Figure 3-4 allow one to calculate a lung cancer risk per unit of asbestos exposure (in f-y/ml) from the linearly rising portion of the curve, the slope of which is 0.16 per year or 0.07 per f-yr/ml (for an exposure intensity of 15 f/ml). However, the data of Figure 3-4 utilized BE (best estimates) in establishing lung cancer mortality. Adjusting to DC (death certificate) diagnosis reduces the value of K_L from 0.011 to 0.0094 ($0.011 \times 3.06/3.60$). The statistical uncertainty on the estimate of risk is very low. However, there is no independent indication that the use of U.S. mortality rates is appropriate. Hammond et al. (1979a) reported that 53.5 percent of insulation workers were current cigarette smokers, 27.3 percent were past smokers, and 17.2 percent never smoked cigarettes. The corresponding data for the 1967 U.S. population were 49.1 percent current smokers, 23.6 percent past smokers, and 27.3 percent non-cigarette smokers (Harris, 1979). This difference would only affect the underlying rates by about 10 percent. However, because insulation workers may have smoked more cigarettes, we will reduce the value of K_L by 20 percent to 0.0075.

3.9.12 Asbestos Products Manufacturing, United States (Chrysotile and Crocidolite); Henderson and Enterline (1979)

The data of Henderson and Enterline (1979) (Figure 3-1 and Table 3-24) can also be used to establish fiber dose-response data even though their data were presented in terms of total dust concentrations measured in millions of particles per cubic foot (mppcf). No data exist on the conversion between mppcf and f/ml for most of the plants studied. However, there are data on the relationship between fiber and total dust concentrations in textile operations and asbestos cement production. Dement et al. (1982) found that conversion of 3 f/ml/mppcf was appropriate to most textile operations, although Ayer et al. (1965) had earlier suggested a value of 6 f/ml/mppcf. In a plant making asbestos cement pipe and sheets, Hammad et al. (1979) determined the conversion value to be 1.4. It would be expected that the cement products value would be most applicable to the Henderson and Enterline circumstance because of the extensive use of cement and other mineral particles (e.g., calcium silicate, talc, SiO_2 , MgO) in asbestos products manufacturing. The least squares weighted regression line of SMR on dose is $\text{SMR} = 143 + 0.51 \times \text{mppcf-y}$ (see Table 3-24). Using a value of 1.5 f/ml/mppcf to represent the conversion relationship, the estimate of K_L is 0.0034 (0.51/100/1.5).

TABLE 3-24. LUNG CANCER RISKS, BY DOSE, AMONG RETIREES
OF U.S. ASBESTOS PRODUCTS MANUFACTURERS
(Henderson and Enterline, 1979)

Exposure in mppcf-y	SMR
62 (<10)	197.9 (19) ^a
182 (10-19)	180.0 (9)
352 (20-39)	327.6 (19)
606 (40-79)	450.0 (9)
976 (>80)	777.8 (7)
Complete cohort:	270.4 (63)

Estimated average cumulative exposure: 249 mppcf-y.

^a() = number of deaths.

Regression equations

$$\begin{aligned} \text{SMR} &= 143 + 0.51(\pm 0.13) \times \text{mppcf-y} && \text{weighted} \\ \text{SMR} &= 100 + 0.66(\pm 0.07) \times \text{mppcf-y} && \text{unweighted} \end{aligned}$$

Weighted regression equation forced through an SMR of 100:

$$\text{SMR} = 100 + 0.64 (\pm 0.097) \times \text{mppcf-y}$$

As described previously, observing a cohort beginning at age 65 may seriously understate the full impact of asbestos exposure. Most of the workers in this cohort began employment prior to age 25. To partially account for selection effects among retirees, we will multiply the above value by 1.45. [This adjustment is the ratio of the lifetime mortality from age 25 to lifetime mortality at age 65 (see Table 3-8)]. Thus, K_L is adjusted to a value of 0.0049.

3.9.13 Asbestos Cement Products, United States (Chrysotile and Crocidolite); Weill et al. (1979); Hughes and Weill (1980)

A study of an asbestos cement production facility also provides exposure-response information (Weill et al., 1979; Hughes and Weill, 1980), as shown in Table 3-25. Although the experience of 5645 individuals was reported, 1791 of whom had been employed for longer than two years, the dose-response information is uncertain because of limitations in the mortality data. Of even greater significance, tracing was accomplished through information supplied on vital status by the Social Security Administration, and this information only allowed the vital status of 75 percent of the group to be determined. Those individuals untraced were considered alive in the analyses, which assumption may have led to serious misestimates of mortality because prior to 1970, many deaths, particularly of blacks, were not reported to the Social Security Administration. The percentage of unreported deaths of both sexes ranged from nearly 80 percent in 1950 to 15 percent in 1967 (Aziz and Buckler, 1980). Thus, many cohort members could be deceased, a fact unknown to the researchers. This could likely be the source of the extraordinarily low overall reported mortality of the cohort, which allowed deficits of about 40 percent in several exposure categories. (The overall SMR is 68.)

Two methods of adjustment for incomplete trace can be made. In one, the overall SMR for lung cancer is divided by the SMR for causes other than lung and gastrointestinal cancer (66). This yields a value of $K_L = 0.0064$, using a value of 64 mppcf for the group exposure and a fiber-particle conversion factor of 1.4 (Hammad et al., 1979) [$((104/66)-1)/64/1.4$]. Alternatively, a regression of SMR on dose yields $SMR = 70 + 0.43 \times mppcf-y$. The low value of SMR is probably the result of missing deaths. If the percent missing is similar in each category then $K_L = 0.0042$ ($0.43/100/1.4/0.70$). We will use the average of these values, 0.0053, for the point estimate of K_L . The assumption that there is an equal percentage of missing deaths in each category is

TABLE 3-25. LUNG CANCER RISKS, BY DOSE, AMONG ASBESTOS CEMENT PRODUCTION WORKERS (Weill et al., 1979)

Exposure in mppcf-y ^a	SMR	RR ^b
5 (<10)	77 (19) ^c	1.00
25 (11-50)	70 (8)	1.14
75 (51-100)	26 (1)	0.52
150 (101-200)	290 (9)	2.85
400 (>200)	226 (14)	2.75
	104 (51)	

Estimated average cumulative exposure: 63.6 mppcf-y

^aAccumulated during first 20 years from initial employment.

^bRelative risk from an internal case-control analysis.

^c() = number of deaths.

Regression equations

$$\begin{aligned} \text{SMR} &= 70 + 0.43(\pm 0.22) \times \text{mppcf-y weighted} \\ \text{SMR} &= 77 + 0.46(\pm 0.31) \times \text{mppcf-y unweighted} \end{aligned}$$

$$\begin{aligned} \text{RR} &= .96 + 0.47(\pm 0.18) \times \text{mppcf-y weighted} \\ \text{RR} &= .99 + 0.50(\pm 0.26) \times \text{mppcf-y unweighted} \end{aligned}$$

Weighted regression equation forced through an SMR of 100:

$$\text{SMR} = 100 + 0.31(\pm 0.22) \times \text{mppcf-y}$$

uncertain. There are more untraced in the lowest category but a greater percentage of those untraced in the most exposed group may be deceased. If one considers all of the untraced deaths to be in the lowest exposure categories and forces a regression line through the origin, its slope is 0.0040. These uncertainties in possible methods of adjusting for untraced deaths are indicated in Figure 3-7.

3.9.14 Asbestos Cement Products, Ontario, Canada (Chrysotile and Crocidolite); Finkelstein (1983)

A recent study by Finkelstein (1983) also relates mortality in an asbestos cement products facility to measured exposures. He established a cohort of 241 production and maintenance employees from records of an Ontario asbestos cement factory, consisting of all individuals who had nine or more years of

employment beginning prior to 1960. Their mortality experience was followed through October 1980. Impinger particle counts of varying degrees of comprehensiveness were available from various sources (government, insurance company, employer) from 1949 until the 1970s. After 1973, membrane fiber counts were taken. Individual exposure estimates were constructed based on recent fiber concentrations at a particular job. They were modified for earlier years due to changes in dustiness of the job, as determined by the impinger particle counts. These counts were thought to be accurate to within a factor of 3-5. Examples of exposure estimates for the years 1948-1954 for willow operators, forming machine operators, and lathe operators were 40 f/ml, 16 f/ml, and 8 f/ml, respectively.

The lung cancer mortality data are shown in Table 3-26. The dose-response relationship is anomalous. The first two exposure categories show the risk increasing steeply with exposure, but in the last category it falls significantly. Both GI cancer and mesothelioma show a strong positive trend with exposure, suggesting that the exposure rankings are correct. The only regression line that makes sense is one forced through an RR of 1 at zero exposure. This yields a K_L of 0.048, which is close to that calculated from the overall mortality excess and average group exposure. The average cumulative 18-year exposure for the production group in the asbestos cement work was 112.5 f-y/ml. Lung cancer deaths observed in this group were 17 versus 2.0 expected from Ontario rates for an SMR of 850. This yields a value of $K_L = 0.067 [(850-100)/112.5/100]$ which will be used as the estimate from this study.

We do not know the reasons for the very significant difference in risk seen in two plants (of the same company) producing the same product. The point estimate of risk from Finkelstein (1983) ($K_L = 0.067$) is 13 times that of Weill et al. (1979) ($K_L = 0.0053$) even after attempting to correct for the incomplete trace of the latter study. Data on the duration of exposure are not given by Finkelstein (1983), but it would appear that the estimated average fiber exposure of his cohort was between 7 f/ml and 12 f/ml. (The average cumulative exposure over 18 years was 112 f-y/ml; all cohort members were employed for at least 9 years, one of which must have been in an asbestos work area.) This average concentration is about half of that estimated by Weill et al. (1979), using the particle-to-fiber conversion of Hammad et al. (1979). It is not possible to evaluate the accuracy of either set of exposure estimates. The exposure estimates of Finkelstein (1983) were submitted to company officials who thought they were reasonable; but worker descriptions of plant

TABLE 3-26. LUNG CANCER RISKS, BY DOSE, AMONG
ONTARIO ASBESTOS CEMENT WORKERS
(Finkelstein, 1983)

Exposure in f-y/ml	Standardized mortality deaths/1000 p-y Lung Cancer
Ontario	1.6
44	13.6 (5) ^a
92	92.1 (7)
180	11.9 (6)
Complete cohort:	850 (17)

Estimated average cumulative exposure: 112 f-y/ml.

^a() = number of deaths.

Regression equations
(Forced through the value 1.6 at zero exposure)

Lung cancer RR = $1.60 + 0.077 \times \text{f-y/ml}$ weighted
Lung cancer RR = $1.60 + 0.108 \times \text{f-y/ml}$ unweighted

conditions suggest that very high exposures occurred periodically (Ontario Royal Commission, 1984). In a study of asbestosis in the Ontario plant (Finkelstein, 1982), data comparable to that of Berry et al. (1979) were obtained. Finkelstein observed prevalence rates of asbestosis of 4 percent and 6 percent at 50-99 f-y/ml and 100-149 f-y/ml versus 2.5 percent and 8.5 percent by Berry et al. (1979). Henderson and Enterline (1979) observed SMRs of 231 and 522 among retirees of cement sheet and shingle workers and cement pipe workers, respectively. These values are more consistent with the higher risk of Finkelstein (1983) than the lower one of Weill et al. (1979). In Figure 3-7, a fivefold downward uncertainty is indicated in K_L to reflect the maximum stated uncertainty in the exposure estimates of Finkelstein (1983).

3.9.15 Lung Cancer Risks Estimated in Other Reviews

A number of other individuals or groups have also estimated unit exposure risks for lung cancer from these same epidemiological studies. These are shown in Table 3-27. Because of general agreement on the appropriate model for lung cancer, the unit exposure risks estimated in this document are very

TABLE 3-27. COMPARISON OF ESTIMATED LUNG CANCER RISKS BY VARIOUS GROUPS OR INDIVIDUALS IN STUDIES OF ASBESTOS-EXPOSED WORKERS

Study	This Document	Percent increase in lung cancer per f-y/ml of exposure (100 x K _i)					Doll and Peto (1985) f-y/ml	Doll and Peto (1985) f-y/ml
		CPSC ^a	NAS ^b	Royal Commission ^c	and Hanley mppcf-y	Liddell		
Dement et al. (1983b)	2.8	2.3	5.3	4.2	6.9	2.4		
McDonald et al. (1983a)	2.5				5.9	2.0		
Peto (1980) after 1950 before 1951	1.1	1.0	0.8 0.07	1.0				1.25 1.5 0.54 ^d
McDonald et al. (1983b)	1.4				5.1	1.7		
Berry and Newhouse (1983)	0.058	0.06		0.058	0.00	0.00		
McDonald et al. (1984)	0.010				0.00	0.00		
McDonald et al. (1980)	0.06	0.06	0.06	0.020-0.046	0.16	0.05		
Nicholson et al. (1979)	0.17	0.12	0.15					
Rubino et al. (1979)	0.075	0.17						
Seidman (1984)	4.3	6.8	9.1 ^e		3.3 ^e	1.1		
Seikoff et al. (1979)	0.75	1.0	1.7	1.0	3.7	1.2		
Henderson and Enterline (1979)	0.49	0.50	0.3	0.069	0.35	0.23		
Weill et al. (1979)	0.53	0.31			0.66	0.47		
Finkelstein (1983)	6.7	4.8		4.2 ^f				
Newhouse and Berry (1979) Males			1.3					
Females			8.4					
Values used for risk extrapolation		0.3-3.0	2.0	0.02-4.2				1.0
Geometric mean of all studies	0.65							
Geometric mean excluding mining and milling	1.0							

^aU.S. Consumer Product Safety Commission (1983).^bNational Academy of Sciences (1984).^cOntario Royal Commission (1984).^dAll men employed after 1932.^eData from Seidman et al. (1979).^fUnpublished data supplied to the Commission.

similar to those estimated by others. The differences in the values lie in the choice of the method to obtain a dose-response relationship and the treatment of potential biases in a study.

3.9.16 Summary of Lung Cancer Dose-Response Relationships

The results of all the determinations of K_L , the fractional increases in lung cancer risk per f-y/ml exposure, are displayed in Figure 3-7, along with estimates of statistical variation, adjustments for possible biases, and estimates of uncertainties associated with exposure determinations. The details of the calculations of statistical uncertainty are provided in Table 3-10, which also shows that the confidence limits associated with an individual value of K_L are large. The uncertainties are largely the result of statistical variations associated with small numbers and uncertainties in exposure measurements. However, statistical variabilities appear to be more important. In 9 of the 14 studies, uncertainties in the measure of response contribute more to the overall uncertainties than do uncertainties in the measure of exposure. Three studies have 95 percent confidence limits of about two orders of magnitude.

Figure 3-7 displays the unit exposure risks in 14 studies, by predominant fiber type in the exposure and by industrial process. Table 3-28 lists the geometric mean of the unit exposure risks, estimated for the different industrial processes, showing substantial differences in the risks observed, even between processes using predominantly the same asbestos mineral. Significantly lower unit exposure risks ($p < 0.05$) are associated with chrysotile mining and milling and friction product manufacturing compared to the other three processes studied. However, because of the great uncertainty associated with the unit exposure risks in friction products manufacturing, the level of significance of the difference is less than for mining and milling.

There is reasonable agreement between the unit risks observed in different studies within a given industrial process. In the case of textile production, even though the cohorts studied by Peto (1980) and McDonald et al. (1983b) were exposed to some quantities of crocidolite, the unit risks were very similar to that of the plant studied by Dement et al. (1983b) and McDonald et al. (1983a). The only substantial difference in the four groups exposed to mixed fibers in manufacturing processes is the high unit risk observed in the study of Finkelstein (1983). Whether this is real or the result of uncertainties in the study cannot be established at this time. There is no statistical

TABLE 3-28. WEIGHTED GEOMETRIC MEAN VALUES AND ESTIMATED 95 PERCENT CONFIDENCE LIMITS ON K_L FOR THE VARIOUS ASBESTOS EXPOSURE CIRCUMSTANCES DEPICTED IN TABLE 3-10 AND FIGURE 3-7.

Asbestos process or use	Fiber exposure	Geometric mean value of K_L	95% confidence interval
Textile production	Predominantly Chrysotile	0.020	(0.0096 - 0.042)
Friction products manufacturing	Chrysotile	0.00023	(0.00010 - 0.0051)
Mining and milling	Chrysotile	0.00098	(0.00028 - 0.0034)
Amosite insulation production	Amosite	0.043	(0.0084 - 0.074)
Mixed product manufacturing or use	Amosite Chrysotile Crocidolite	0.0068	(0.0035 - 0.013)
All processes	Amosite Chrysotile Crocidolite	0.0065	(0.0025 - 0.017)
All processes except mining and milling	Amosite Chrysotile Crocidolite	0.010	(0.0040 - 0.027)
Textile production and mixed product manufacturing or use	Amosite Chrysotile Crocidolite	0.013	(0.0074 - 0.024)

difference in the unit exposure risk seen in the group exposed only to amosite asbestos compared to those exposed predominantly to chrysotile in textile production or to mixed fibers in manufacturing.

The origin of the differences in unit exposure risks between mining and milling and other chrysotile exposure circumstances is not completely clear. It was suggested by many individuals, including McDonald et al. (1984), that the differences between mining and milling and various production processes may be related to differences in the fiber size distributions. As in the review of experimental studies (Chapter 4), fiber length and diameter strongly affect the potential for fibers to produce mesothelioma. Corresponding data are not

available for lung cancer, but it would be expected that different fiber size distributions would produce different responses. There are many long and curly fibers present in the environment of miners and millers which are easily counted, but not easily inspired because of their large equivalent diameter. In asbestos-using industries, as fibers are broken apart a greater percentage are deposited in the lung. Many of these will remain within a carcinogenic size range. However, the number counted by the membrane filter procedure compared to the number that are potentially carcinogenic may substantially decrease in such circumstances.

As shown in Table 3-28, the geometric mean value of K_L , using data from all studies, is 0.0065, and that for all studies exclusive of mining and milling is 0.010. Because the mining and milling exposures (long and curly fibers, preprocessed) are likely to be less typical of those experienced in the environment (processed, see also Sections 3-8, 3-9, 3-17, 4-2, and 5-1 to 5-8), the best estimate for the fractional increased risk of lung cancer, K_L , for environmental asbestos exposures appears to be 0.010. This value is the same as that used by the Occupational Safety and Health Administration in their risk assessment for the proposed revision to the asbestos standard (OSHA, 1983). OSHA's analysis also was based on risks in studies other than chrysotile mining and milling. The value is one-half that which was adopted by the National Academy of Sciences in their risk analysis (National Academy of Sciences, 1984). The NAS value was based on rounding upward, to 0.02, a median risk of 0.011 estimated in a group of 11 epidemiological studies.

The 95 percent confidence limits on the value 0.010 for K_L are from 0.0040 to 0.027 (a factor of 2.5). This is the result of the analysis of variance in 11 separate estimates. The 95 percent confidence limits on the value of K_L that might be measured in any unstudied exposure circumstance is estimated to be a factor of 10 (8.3 by calculation). The range of uncertainty may, in fact, be greater than the 10 fold factor estimated here, but insufficient information exists by which to make any more precise or definite estimate.

3.10 TIME AND AGE DEPENDENCE OF MESOTHELIOMA

In contrast to lung cancer, for which a relative risk model well explained the data, mesothelioma is best described by an absolute risk model in which the incidence is independent of the age at first exposure and increases according to a power of time from onset of exposure. The rationale for such a model

describing human carcinogenesis was discussed by several authors (e.g., Armitage and Doll, 1961; Pike, 1966; Cook et al., 1969). Such a model was utilized by Newhouse and Berry (1976) in predicting mesothelioma mortality among a cohort of factory workers in England. Specifically, they matched the incidence of mesothelioma to the relationship

$$I_M = c(t - w)^k \quad (3-4)$$

where I_M is the mesothelioma incidence at time t from onset of exposure, w is a delay in the expression of the risk, and c and k are empirically derived constants. The incidence of asbestos-induced mesothelioma in rats (Berry and Wagner, 1969) followed this time course. In the case of the analysis of Newhouse and Berry (1976), the data suggested that the value of k was between 1.4 and 2 and w between 9 and 11 years. However, the relatively small number of cases available for analysis led to a large uncertainty in the values estimated for either k or w . Peto et al. (1982) recently analyzed mesothelioma incidence in five groups of asbestos-exposed workers. In one study analyzed, that of Selikoff et al. (1979), the number of cases of mesothelioma were sufficiently large that the age dependence of the mesothelioma risk could be investigated. Peto et al. (1982) showed that the absolute incidence of mesothelioma was independent of the age at first exposure and that a function, $I_M = ct^{3.2}$ (see Equation 3-4), fit the data well between 20 and 45 years from onset of exposure. However, observed incidence rates for earlier times were less than those projected, and the authors suggested that an expression proportional to $(t - 10)^2$ better fit the data up to 45 years from onset of exposure. The analysis of Peto et al. (1982) excluded individuals first employed before 1922 and after 1946 and over the age of 80; the fit to the mortality of the entire group suggested a value of k of about 5.

Figure 3-8 shows the risk of death of mesothelioma, according to age, for individuals first exposed between ages 15 and 24 and between ages 25 and 34. As can be seen, these data, although somewhat uncertain because of small numbers, are roughly parallel and separated by 10 years, as was the relative risk for lung cancer. Thus, the absolute risk of death from mesothelioma appears to be directly related to onset of exposure and is independent of the age at which the exposure occurs. The risk of death from mesothelioma among the insulation workers is plotted, according to time from onset of exposure, on the right side of Figure 3-8. It increases to 40 years from onset of exposure. Thereafter, the increase is less. There is even a decrease in the

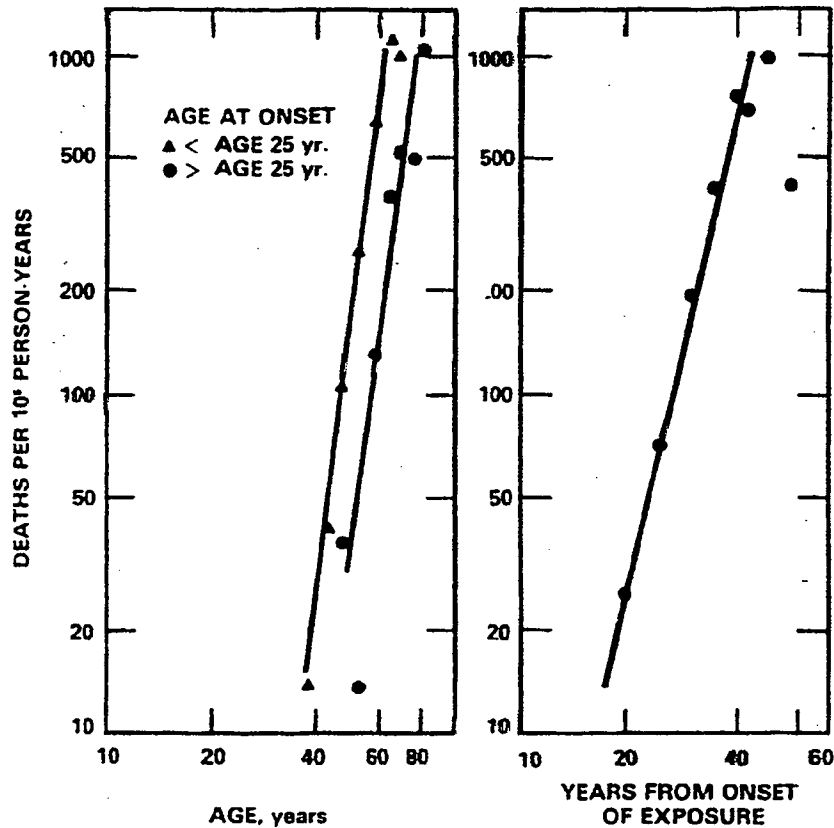


Figure 3-8. The risk of death from mesothelioma among insulation workers according to age and years from onset of exposure. The risk of death according to age is shown separately for insulators first employed before age 25 and after age 25. Data supplied by I.J. Selikoff and H. Seidman. Source: Nicholson et al. (1982).

risk at 50+ years from onset. This can be the result of misdiagnosis of the disease in individuals age 75 and older, statistical fluctuations associated with small numbers, or selection factors also seen in the risk of lung cancer (e.g., those who lived to age 80 may have had jobs with much lower exposure).

The graph of Figure 3-8 is also represented by an equation of the form

$$I_M = c \cdot f(t-w)^{k+1} \quad (3-5)$$

The data of Figure 3-8, however, are not sufficient to separately specify w and k . If w is 0, k lies between 4 and 5. If w is 10, k lies between 2 and 3. To estimate the risk from long-term exposures, consider an exposure of duration d that began T years ago. The incidence of mesothelioma at time t from the entire exposure is

$$I_M = c \cdot f \cdot \int_{T-d}^T (t-10)^k dt \quad (3-6a)$$

assuming a delay of 10 years. The choice of a delay of 10 years is indicated by the data on lung cancer risk, where a delay of from 5 to 10 years was observed between asbestos exposure and the manifestation of risk. f is the intensity of the asbestos exposure, and as used in Equation 3-6, assumes a linear relationship between intensity of exposure and risk (see Figures 3-4 and 3-5). Equation 3-6 is also linear in dose for short duration exposures. Equation 3-6 yields

$$\begin{aligned} I_M &= \frac{c}{k+1} \cdot f \cdot [(t-10)^{k+1}]_{T-d}^T \\ &= \frac{c}{k+1} \cdot f \cdot [(T-10)^{k+1} - (T-d-10)^{k+1}] \end{aligned} \quad (3-6b)$$

Using a value of $k = 2$ (which best fits the workers' data) and letting $c/k+1 = K_M$ leads to the following relations for varying times of exposure:

$$I_M(t,d,f) = K_M \cdot f[(T-10)^3 - (T-10-d)^3] \text{ for: } T > 10+d \quad (3-6c)$$

$$= K_M \cdot f(T-10)^3 \text{ for: } 10+d > T > 10 \quad (3-6d)$$

$$= 0 \text{ for: } 10 > T \quad (3-6e)$$

Here I_M is the mesothelioma incidence at t years from onset of exposure to asbestos for duration d at a concentration f . K_M is carcinogenic potency and may depend on fiber type and dimensionality. Note that I_M depends only upon exposure variables and not upon age or calendar year period.

K_M is the measure of the mesothelioma risk per year. In order to calculate the full effect of an asbestos exposure on an exposed population over time, the calculated incidence per year must be summed for each interval from onset of exposure. In such a calculation, it is necessary to take account of the mortality that occurs in the exposed population as it ages. In practice, such calculations, are carried out by 5-year age and onset of exposure intervals.

3.11 QUANTITATIVE DOSE-RESPONSE RELATIONSHIPS FOR MESOTHELIOMA

Four studies provide information on the incidence of mesothelioma (pleural and peritoneal combined) according to time from onset of exposure, and contain data that allow estimates to be made of the duration and intensity of asbestos exposure. These data are given in Table 3-29. Values for K_M , the potency factor for mesothelioma risk, can be estimated using Equations 3-6c, 3-6d, and 3-6e. Other studies reported cases of mesothelioma, but incidence data are lacking or simply not provided. In others, the data were not given because very few mesothelioma deaths were seen. Thus, some studies with missing data could have a lower value of K_M . Note that we are estimating values of K_M from a biased sample of those studies in which K_L was estimated. A measure of the bias can be estimated by comparing the values of K_M and K_L obtained in each analysis with an analysis of the percentage of deaths from mesothelioma compared to excess lung cancer in other studies. The estimate of K_M for each of the four studies was made by calculating a relative mesothelioma incidence using Equation 3-6 and data on duration and intensity of asbestos exposure. The relative incidence curves were then superimposed on the observed incidence data in each study to obtain the value of K_M . These fits are depicted on Figures 3-9 and 3-10. The four studies are described below and summary data are listed in Table 3-30.

TABLE 3-29. MESOTHELIOMA INCIDENCE BY YEARS FROM ONSET OF EXPOSURE, IN FOUR STUDIES

Years from onset of exposure	Incidence (cases/10,000 person-years)	
	Insulation workers Peto et al. (1982)	Textile workers Peto (1980)
15 - 19	1.2 (2,3) ^a	0.0
20 - 24	3.2 (7,6)	5.7 (1,0)
25 - 29	15.4 (18,29)	13.4 (2,0)
30 - 34	28.9 (16,34)	23.9 (2,0)
35 - 39	52.6 (20,26)	39.4 (2,0)
40 - 44	56.9 (6,19)	
45 - 49	108.1 (14,18)	
50+	66.4 (4,14)	
	Amosite factory workers Seidman (1984)	Asbestos cement workers Finkelstein (1983)
15 - 19	0.0	8.5 (1)
20 - 24	7.4 (1,1)	37.7 (4)
25 - 29	26.2 (3,2)	90.9 (5)
30 - 34	50.8 (4,4)	96.2 (1)
35 - 39	18.4 (0,2)	
40 - 44		
45 - 49		
50+		

^a(,) = number of pleural and peritoneal deaths, respectively.

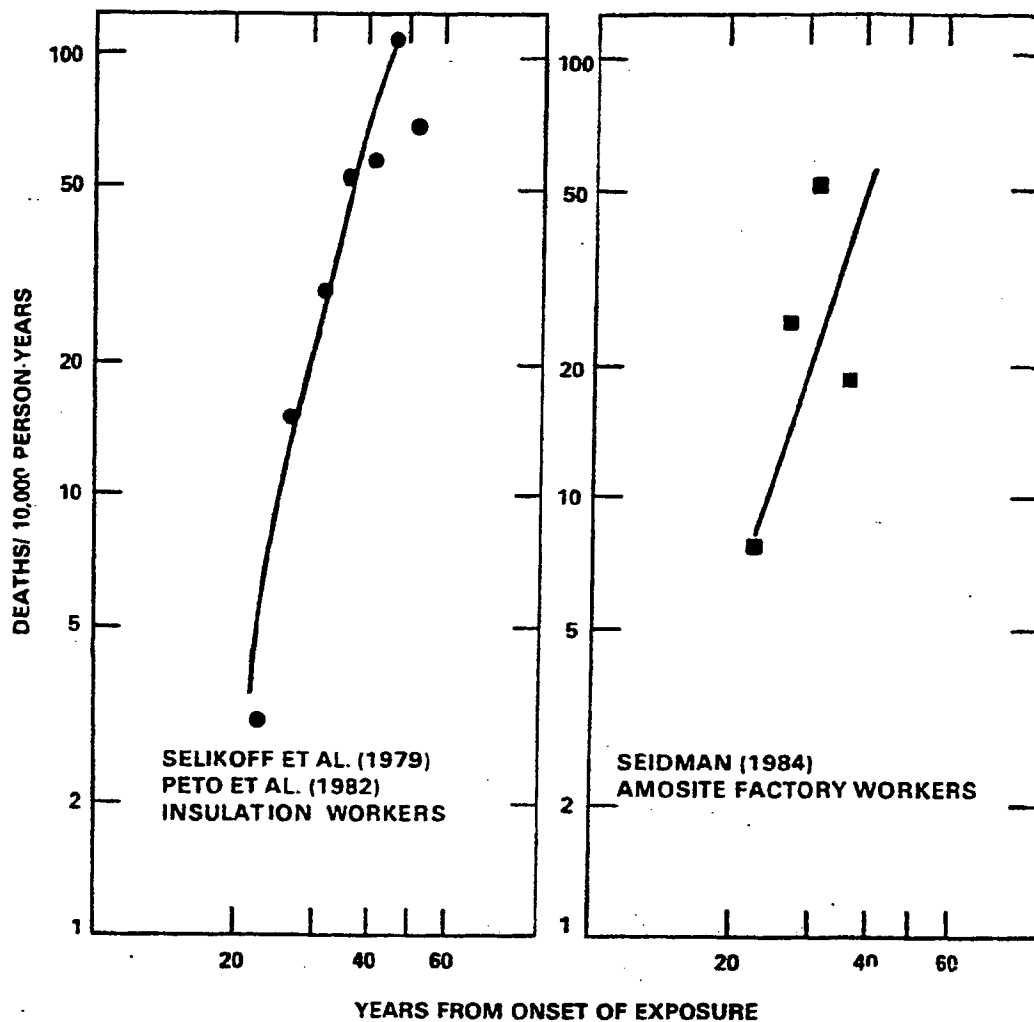


Figure 3-9. The match of curves calculated using Equation 3-6 data on the incidence of mesothelioma in two studies. The fit is achieved for $K_M = 1.5 \times 10^{-8}$ for insulators data and $K_M = 3.2 \times 10^{-8}$ for the amosite workers data.

Source: Peto et al. (1982); Selikoff et al. (1979); Seidman (1984).

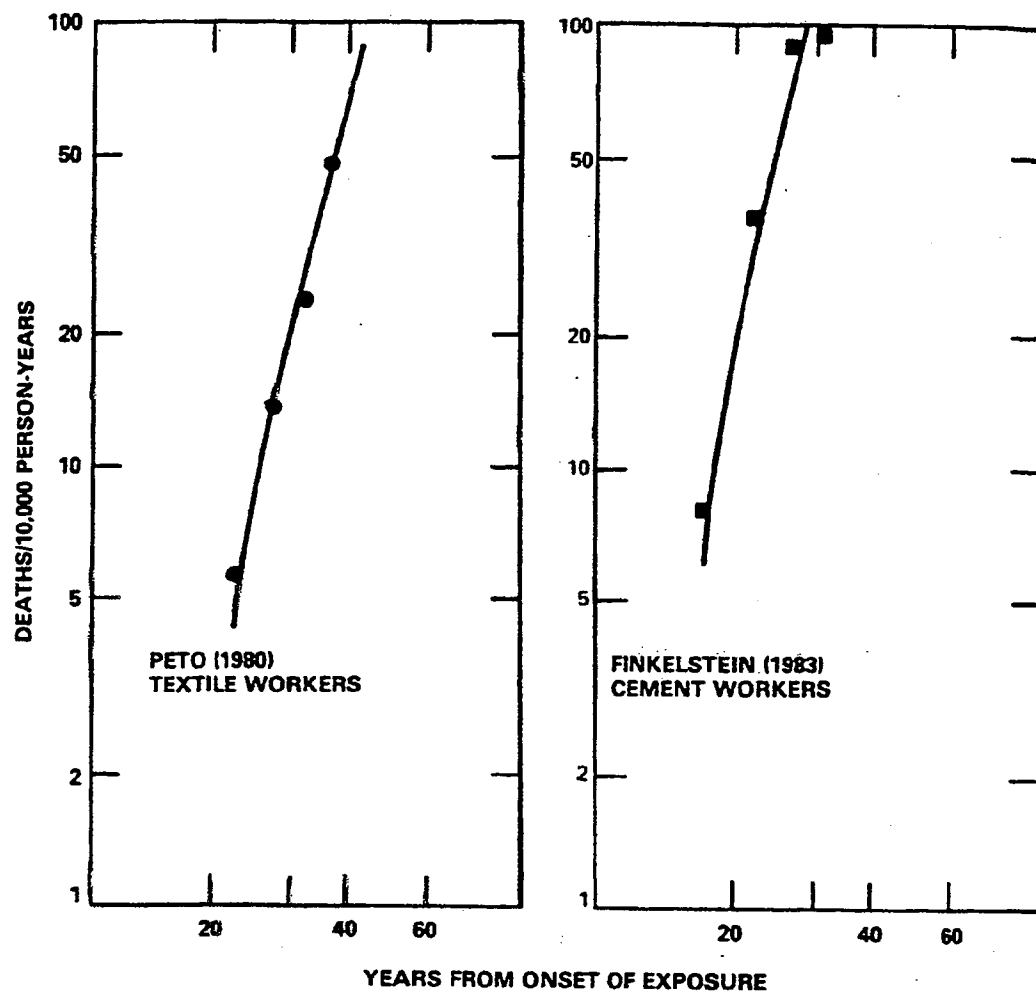


Figure 3-10. The match of curves calculated using Equation 3-6 to data on the incidence of mesothelioma in two studies. The fit is achieved for $K_M = 1.0 \times 10^{-8}$ for the textile workers data and $K_M = 1.2 \times 10^{-7}$ for the cement workers data.

Source: Peto (1980); Finkelstein (1983).

TABLE 3-30. SUMMARY OF THE DATA K_M , THE MEASURE OF MESOTHELIOMA RISK PER FIBER EXPOSURE, IN FOUR STUDIES OF ASBESTOS WORKERS

Study	Average employment duration	Average exposure, f/ml	K_M	K_M/K_L
Insulation workers (Selikoff et al., 1979; Peto et al., 1982)	25	15	1.5×10^{-8}	2.0×10^{-6}
Textile workers (Peto, 1980; Peto et al., 1982)	25	20	1.0×10^{-8}	0.9×10^{-6}
Amosite factory workers (Seidman, 1984)	1.5	35	3.2×10^{-8}	0.7×10^{-6}
Cement factory workers (Finkelstein, 1983)	12	9	1.2×10^{-7}	1.8×10^{-6}

3.11.1 Insulation Application; Selikoff et al. (1979); Peto et al. (1982)

A follow-up through 1979 of the cohort of insulation workers provides data on the incidence of mesothelioma with time from onset of exposure (Peto et al., 1982). It was estimated that their time-weighted average exposure was 15 f/ml (Nicholson, 1976a). Using these data and 25 years for their average duration of exposure, a value of $K_M = 1.5 \times 10^{-8}$ is estimated.

3.11.2 Amosite Insulation Manufacturing; Seidman et al. (1979)

The average employment time of all individuals in this factory was 1.46 years. This value and the previously used value of 46 f/ml for the average exposure yields an estimate for K_M of 3.2×10^{-8} .

3.11.3 Textile Products Manufacturing; Peto (1980); Peto et al. (1982)

A 20-30 f/ml value for exposure intensity is suggested by data presented by Peto (1980). However, some uncertainty exists regarding this value because of discrepancies in relative exposures measured by personal samplers and static samplers. If exposures measured by personal samplers are less than static samplers, as suggested by the data of Smither and Lewinsohn (1973), the average exposure could be about 15 f/ml. Using 20 f/ml and an employment period of 25 years, a value of $K_M = 1.0 \times 10^{-8}$ is estimated.

3.11.4 Asbestos Cement Products, Ontario, Canada; Finkelstein (1983)

The cumulative exposure of the cohort over 18 years was 112 f/yr. Only men with nine or more years of employment were included in the cohort. Although data on the exact duration and intensity of exposure are unavailable, we will use a value of 12 years for duration of exposure and 9 f/m for the intensity of exposure. This yields a value of $K_M = 1.2 \times 10^{-7}$.

3.11.5 Other Studies

A note on the friction product studies is appropriate. In the study of Berry and Newhouse (1983) little excess lung cancer risk was observed (see Section 3.9.5). Eleven deaths from mesothelioma occurred. A comparison of the work histories of the cases and 40 controls matched for sex, age, and date of hire showed an increased probability of crocidolite exposure among the cases (eight had such exposure) and an increased probability of heavy chrysotile exposure. In the study of McDonald et al. (1984), an elevated risk of lung cancer was observed but no trend with increasing exposures (see Section 3.9.6). McDonald et al. (1984) did not find any mesothelioma deaths among the cohort members. However, three mesothelioma deaths among former plant employees were reported to the Connecticut Tumor Registry (Teta et al., 1983). Two were in women and one in a male who terminated employment prior to receiving a Social Security number and, thus, all were excluded from the cohort of McDonald et al. (1984). Mention of the mesotheliomas is important because it illustrates that cases can occur from chrysotile exposures in friction products manufacture. Because of the low observed lung cancer dose-response relationship in both the studies of McDonald et al. (1984) and Berry and Newhouse (1983), no meaningful data on mesothelioma risk relative to lung cancer can be obtained.

3.11.6 Summary of Mesothelioma Dose-Response Relationships

A review of the four studies for which values of K_M were obtained indicate that three are very similar while K_M from the study of Finkelstein (1983) is much higher. This was also found in the value of K_L estimated in that study. Much closer agreement exists in the ratio of K_M/K_L . While it is not possible to make an accurate estimate of the value of K_M in the 10 other studies used to estimate K_L , a rough measure of mesothelioma risk can be obtained by calculating the ratio of the number of mesothelioma deaths to total deaths and dividing by the cumulative exposures of the groups. This is done in Table 3-31.

TABLE 3-31. ESTIMATE OF A MEASURE OF MESOTHELIOMA RISK RELATIVE TO LUNG CANCER RISK, IN 14 STUDIES

Study	Column 1 Calculated $K_H (\times 10^6)$	Column 2 K_L	Column 3 Cumulative exposure (f-y/ml)	Column 4 Mesothelioma deaths Total deaths	Column 5 $\frac{\text{Col. 4} \times 10^6}{\text{Col. 3}}$	Column 6 $\frac{\text{Col. 5}}{\text{Col. 2} \times 10^2}$	Column 7 K_H/K_L
<u>Textile Production</u>							
Dement et al., 1983b		0.028	43.9	0.0041	0.91	0.33	
McDonald et al., 1983a		0.025	30.9	0.0018	0.58	0.23	
Peto, 1980	1.0	0.011	500	0.040	0.80	0.73	0.91×10^{-6}
McDonald et al., 1983b		0.014	50.7	0.016	3.16	2.25	
<u>Friction Products</u>							
Berry & Newhouse, 1983		0.00058	37.1	0.0060	1.62	27.9	
McDonald et al., 1984		0.00010	30.9	0.0030 ^a	0.97	97	
<u>Mining and Milling</u>							
McDonald et al., 1980		0.00060	555	0.0030	0.05	0.83	
Nicholson et al., 1979		0.0017	1070	0.0056	0.05	0.29	
Rubino et al., 1979		0.00081	258	0.0045	0.17	2.10	
<u>Amosite Insulation Manufacturing</u>							
Seidman, 1984	3.2	0.043	67.1	0.029	4.26	0.99	0.74×10^{-8}
<u>Insulation Application</u>							
Selikoff et al., 1979	1.5	0.0075	375	0.087	2.32	3.09	2.0×10^{-8}
<u>Asbestos Products Manufacturing</u>							
Henderson & Enterline, 1979		0.0049	373	0.0064	0.17	0.35	
Weill et al., 1979; Weill, 1984		0.0053	89	0.0046 ^b	0.652	0.98	
Finkelstein, 1983	12	0.048	112	0.153	13.66	2.85	1.8×10^{-8}
Geometric means:							
excluding friction products						0.87	
excluding friction products and studies of Dement and Nicholson						1.07	

^aNo mesotheliomas were reported in the male cohort studied. However, three mesotheliomas (two in women) were reported from the workforce of the plant studied (Teta et al., 1983). The rough mesothelioma risk calculation uses these three cases and a value of 1000 for the total mortality in the plant work force.

^bIn 1984 testimony before OSHA, Weill reported 9 mesotheliomas among 1953 deaths in his cohort of cement workers.

Column 5 of Table 3-31 indicates this rough mesothelioma risk in all 14 studies, and Column 6 shows the ratio of this risk to $100 \times K_L$. Note that the two measures of risk are not commensurate. To make this explicit the ratio will be designated as the "relative mesothelioma hazard." The geometric mean of the relative mesothelioma hazard in all studies except friction products manufacturing is 0.87. The ratios in the two friction products studies are very uncertain because of the great uncertainties in the lung cancer risks, and they are not included in the average. Table 3-32 lists the geometric means, by process, of the relative mesothelioma hazards in all studies except Dement et al. (1983b) and Nicholson et al. (1979) (whose mesothelioma cases are included in the larger studies of McDonald et al., 1980, 1983a,b).

The geometric means of the relative mesothelioma hazards, by process, differ very little (excluding consideration of friction products because of the large uncertainties in lung cancer risk.) Textile production, including studies of plants that used some crocidolite and amosite have the lowest average hazard. Product manufacture and use has the highest relative mesothelioma hazard. This is largely the result of the high hazard found among insulation workmen who were exposed only to amosite and chrysotile, but where a review was made of all available pathological material to identify cases. The geometric average of the manufacturing plant studies is 0.99, coincidentally the same as found in amosite insulation manufacture. Chrysotile mining also demonstrated a high relative mesothelioma hazard (although in absolute terms the unit exposure risks for both mesothelioma and lung cancer are lower than other asbestos exposure circumstances). The high relative hazard was, in part, the result of a high relative hazard found in the study of Rubino. Nevertheless, the hazard found in the large study of McDonald et al. (1980), 0.83, is higher than that of textile production (predominantly chrysotile but with some crocidolite and amosite) and little different from all product manufacturing, 0.99, using all types of asbestos. Thus the geometric mean of all studies, 1.07, fairly represents all exposure circumstances, except perhaps, insulation work.

There is no evidence in those studies listed in Table 3-31 and 3-32 that would suggest a substantially different relative mesothelioma hazard for the different types of asbestos varieties. However, this conclusion is limited by the fact that crocidolite was not the dominant fiber exposure in any of the study groups. In an analysis of the risk of pleural and peritoneal mesothelioma relative to excess lung cancer in all published cohorts, including those

TABLE 3-32. ESTIMATED GEOMETRIC MEAN VALUES OF THE RELATIVE MESOTHELIOMA HAZARD (COL. 6 OF TABLE 3-31) FOR THE VARIOUS ASBESTOS EXPOSURE CIRCUMSTANCES LISTED IN TABLE 3-31

	Geometric mean value of relative hazard (Col 6, Table 3-31)
Textiles (except Dement et al., 1983b) ^a	0.72
Friction products	52 ^b
Mining and milling (except Nicholson et al., 1979) ^a	1.32
Amosite manufacturing	0.99
Asbestos product manufacturing and use (crocidolite 0% of insulation, 15% of two factories; 5% of Manville plant)	1.32 ^c
Geometric mean of all except friction products (excluding Dement et al., 1983b, and Nicholson et al., 1979)	1.07
Geometric mean of all except friction products and mining and milling	1.02

^aA single mesothelioma case is included in the larger study of McDonald et al.

^bAn unreasonably high value because of low lung cancer risk.

^cCrocidolite contribution very small and can't extract out relative contribution of crocidolite.

with only crocidolite exposures, it would appear that the ratio of the cases of pleural mesothelioma to excess lung cancers is two to three times greater than that from amosite, chrysotile or mixed fiber exposures. (See Section 3-17, Relative Carcinogenicity of Different Asbestos Varieties.) Considering both pleural and peritoneal sites this ratio increases to three or four times for pure crocidolite exposures. There are no estimates of the relative exposures to crocidolite in those cohorts where such exposure was possible. However, to estimate the possible effect, the relative mesothelioma hazard for the studies of Peto (1980) and McDonald et al. (1983b) were reduced by 20 percent to account for effects of a 2 percent crocidolite usage and those of asbestos

products manufacturing by 50 percent. This yields a geometric mean of 0.85 rather than 1.07. This 26 percent difference for an assumed effect of crocidolite in five studies is far less than the tenfold uncertainty in the estimated values of K_L or K_M for an unstudied exposure circumstance. Because of the absence of any evident effect of crocidolite in the values of relative mesothelioma risk in the Table 3-32 and small estimated crocidolite correction to the relative mesothelioma hazard, no adjustment will be made to the final estimated value of K_M (which have associated with it a twentyfold uncertainty in estimating an unknown exposure risk).

The relative mesothelioma hazard in the four studies for which the geometric mean of K_M was calculated is 1.59. The geometric mean of the relative mesothelioma hazard in all studies (excluding friction products) is 1.07. This suggests that the value of K_M/K_L in the four studies is 49 percent higher than the average for all studies. As the geometric mean of the calculated values of K_M/K_L in the four studies is 1.25×10^{-6} , the above data suggest a value of K_M/K_L for all studies of 0.84×10^{-6} . However, this is certainly a lower limit on the value of the ratio. Firstly, inclusion of the friction products studies would raise it by some (unknown) amount. Secondly, 3 of the 4 studies for which K_M/K_L was calculated used data from all available pathological materials and medical records to identify mesothelioma cases, while those not analyzed generally did not. Had all studies done so, the relative mesothelioma hazard would be higher (in the Seidman, 1984 and Selikoff et al., 1979 studies such review increased the number of mesothelioma cases by 75 percent). To partially account for these factors we will use a value of 1.0×10^{-6} for the ratio of K_M/K_L . The average value of K_M is thus 1.0×10^{-8} .

The 95 percent confidence limits on the estimated value of K_L was a factor of 2.5 and a factor of 10 on its application to any unknown exposure circumstance. Larger uncertainty factors would apply to K_M because the data from which it was estimated are more uncertain than those from which K_L was estimated. While it is not possible to estimate the 95 percent confidence limit directly, a factor of 5 would appear to be reasonable for the average value of K_M and a factor of 20 on its application to any unknown exposure circumstance.

The range of uncertainty may in fact be greater than that suggested. While this 20-fold factor provides a range of 400 (i.e., estimates are divided by 20 and multiplied by 20 to determine the range), the range could be greater

yet. However, insufficient information exists by which to make any more precise or definite estimate of uncertainty.

3.12 ASBESTOS CANCERS AT EXTRATHORACIC SITES

The consistency of an increased cancer risk and its magnitude, either in absolute (observed-expected deaths) or relative (observed/expected deaths) terms is less for cancer at other sites. Nevertheless, many studies document significant cancer risks at various gastrointestinal (GI) sites. Cancer of the kidney and urinary organs was also found to be significantly elevated in two large studies (Selikoff et al., 1979; Puntoni et al., 1979). Among female workers, ovarian cancer was found in excess (Newhouse et al., 1972; Wignall and Fox, 1982; Acheson et al., 1982). While no other specific sites were shown to be elevated at the 0.05 level of significance, the category of all cancers other than the lung, GI tract, or mesothelioma is significantly elevated (e.g., Selikoff et al., 1979).

Table 3-33 lists all studies in which more than 10 GI cancers were expected or observed and in which the overall lung cancer risk was elevated at the 0.05 level of significance. Some studies having statistically uncertain data were eliminated from consideration, as were several larger studies demonstrating a low risk of lung cancer because of exposure or follow-up circumstances. Because the excess risk of GI cancer is less than that of lung cancer, significantly elevated risks are unlikely to be seen in studies that demonstrate little risk of lung cancer; therefore, negative data in such studies do not have much significance. In considering Table 3-33, note that all but 3 of the 23 listed studies show an excess GI cancer risk, even though the risk is small in several studies. However, 10 of the 23 studies demonstrate risk at a 0.05 level of significance. Figure 3-11 displays the relationship between the relative risk of lung cancer and relative risk of GI cancer in the 23 studies in Table 3-33. Figure 3-11 shows there is a consistent relationship between increased GI cancer risk and increased lung cancer risk. Fiber exposure to the GI tract is probable because the majority of fibers inhaled are brought up from the respiratory tract and swallowed (Morgan et al., 1975), and some may become entrapped within the gut wall (Storeygard and Brown, 1977). Additionally, fibers may be swallowed directly. Nevertheless, the magnitude

TABLE 3-33. OBSERVED AND EXPECTED DEATHS FROM VARIOUS CAUSES IN SELECTED MORTALITY STUDIES

	Respiratory cancer			Digestive cancer				Other cancers			
	ICD 162-164			ICD 150-159				ICD except 150-59, 162-6, meso			
	O	E	O-E	O	E	O-E	$\frac{(O-E)^d}{(O-E)^r}$	O	E	O-E	$\frac{(O-E)^d}{(O-E)^r}$
1. Henderson and Enterline (1979)	63	23.3	39.7	55	39.9	15.1	0.380	55	45.6	9.4	0.237
2. McDonald et al. (1980)	230	184.0	46.0	276	272.4	3.6	0.078	237	217.4	19.6	0.426
3. Newhouse and Berry (1979) (male)	103	43.2	59.8	40	34.0	6.0	0.100	38	27.4	10.6	0.177
4. Newhouse and Berry (1979) (female)	27	3.2	23.8	20	10.2	9.8	0.412	33	20.4	12.6	0.529
5. Selikoff et al. (1979) (NY-NJ)	93 ^a	13.1	79.9	43 ^a	14.8	28.2	0.353	28 ^a	24.5	3.5	0.044
6. Selikoff et al. (1979) (U.S.)	390	93.7	296.3	89	53.2	35.8	0.121	184	131.8	52.2	0.176
7. Nicholson et al. (1979)	25	11.1	13.9	10	9.5	0.5	0.036	14	16.1	(2.1)	def.
8. Peto (1977)	51	23.8	17.2	16	15.7	0.3	0.019	18	24.8	(6.8)	def.
9. Mancuso and El-attar (1967)	30	9.8	20.2	15	7.1	7.9	0.527	20	6.8	13.2	0.653
10. Puntoni et al. (1979)	123	54.9	68.1	94	76.6	17.4	0.255	88	81.3	6.7	0.098
11. Seidman et al. (1979)	83	21.9	61.1	28	22.7	5.3	0.087	39	35.9	3.1	0.037
12. Dement et al. (1983b)	33	9.8	23.2	10	8.1	1.9	0.082	11	14.1	(3.1)	def.
13. Jones et al. (1980)	12	6.3	5.7	10	20.3	(10.3)	def.	35	39.5	(4.5)	def.
14. McDonald et al. (1983a)	59	29.6	29.4	26	17.1	8.9	0.302	35	27.7	7.4	0.252
15. McDonald et al. (1984) ^b	73	49.1	23.9	59	51.6	7.4	0.309	70	60.4	9.6	0.402
16. Robinson et al. (1979)	49	36.1	12.9	50	41.4	8.6	0.667	69	51.2	17.8	0.380
17. Acheson et al. (1984)	57	29.1	27.9	19	17.1	1.9	0.068	33	28.2	4.8	0.172
18. Wignall & Fox (1982)	10	3.7	6.3	7	10.7	(3.7)	def.	35	21.6	13.4	2.127
19. Meurman et al. (1974)	21	12.6	8.4	7	14.9	(7.9)	def.	no data			
20. Albin et al. (1984)	12	6.6	5.4	19	10.8	8.2	1.519	21	20.4	0.6	0.111
21. Elmes & Simpson (1977)	24	5	19	13	1	12	0.632	10	no data		
22. Nicholson (1976a)	27 ^a	8.4	18.6	13 ^a	5.0	8.0	0.430	17 ^a	14.4	2.6	0.140
23. Clemmesen & Mjalgrim-Jensen (1981)	44	27.3	16.7	31	29.9	1.1	0.066	89	93.9	(4.9)	def.

O = observed deaths.

E = expected deaths.

d = digestive cancer.

r = respiratory cancer.

o = other cancer.

ICD = International Classification of Diseases.

def. = no ratio when deficient in O-E.

^aBest estimate data on causes of death.^bExcess risk may not be asbestos-related; see Section 3.9.6.

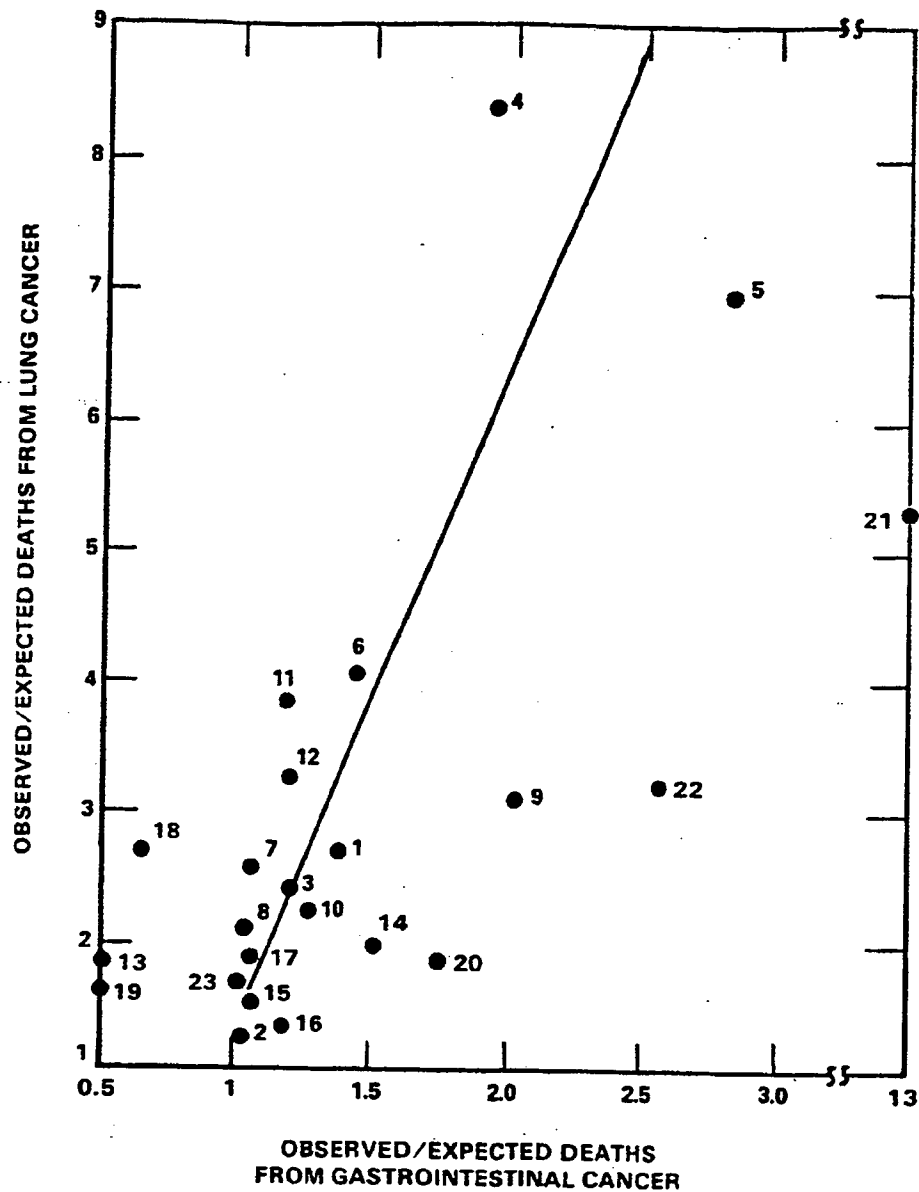


Figure 3-11. The ratio of observed to expected mortality from lung cancer versus the ratio of observed to expected mortality from gastrointestinal cancer.

Source: Table 3-33, reference numbers 1 through 23.

of the excess at GI sites is much less than for the lung. In recent studies, the GI excess is about 10-30 percent of the lung excess.

The number of studies demonstrating a statistically significant excess risk of gastrointestinal cancer in asbestos-exposed groups and the correlation of the relative risk of gastrointestinal with the relative risk of lung cancer are highly suggestive of a causal relationship between asbestos exposure and gastrointestinal cancer. However, alternative interpretations of the above data are possible. Doll and Peto (1985) have suggested that many of the excess cancers attributed to gastrointestinal sites may be misdiagnosed lung cancers or mesotheliomas. They also cite the absence of confirmatory animal data showing a risk of cancer at extrapulmonary sites as weighing against a causal relationship. However, it is difficult to accept that all excess gastrointestinal cancers are the result of misdiagnosis. While cancers of some of the gastrointestinal sites, particularly the pancreas and the stomach to some extent, are often misdiagnosed mesotheliomas, cancers of the colon and rectum are usually correctly certified and the excesses at these sites across studies are unlikely to be the result of misdiagnosis.

The U.S. Environmental Protection Agency Cancer Assessment Group has reviewed studies with GI cancer excess. They have concluded that the association between GI cancer excess and asbestos exposure is strong.

Table 3-33 also lists the observed and expected mortality for cancers other than mesothelioma, the GI, or respiratory tract. The elevation is not as consistent as for GI cancer. Only six studies have elevated risks that are significant at a 0.05 level, and deficits are observed in five. The analysis is further complicated by the possibility that misattribution of lung cancer or mesothelioma may have occurred for some cases. For example, brain or liver cancers could be metastatic lung cancers in which the primary site was not properly identified. In the study of insulation workers, Selikoff et al. (1979) found that 26 of 49 pancreatic cancers were misclassified; most of those misclassified were peritoneal mesotheliomas. The excess at other sites is much less than lung cancer and roughly similar to that of GI cancer.

3.13 ASBESTOSIS

Asbestosis, a long-term disease entity resulting from the inhalation of asbestos fibers, is a chronic, progressive pneumoconiosis. It is characterized by fibrosis of the lung parenchyma, usually radiologically evident only

after ten years from first exposure, although changes can occur earlier following more severe exposures. Shortness of breath is the primary symptom, cough is less common, and signs such as rales, finger clubbing, and weight loss in later stages of the disease appear in a proportion of cases. The disease was first reported eight decades ago (Murray, 1907) and has occurred frequently among workers occupationally exposed to the fiber in ensuing years. Characteristic X-ray changes are small irregular opacities, usually in the lower and middle lung fields, often accompanied by evidence of pleural fibrosis or thickening, and/or pleural calcification. Both the visceral and, more commonly, the parietal pleura may be involved.

Currently, 50-80 percent of individuals in groups with heavy occupational exposures beginning more than 20 years earlier are found to have abnormal X-rays. These include asbestos insulation workers (Selikoff et al., 1965), miners and millers (Nicholson, 1976b), and asbestos factory employees (Lewinsohn, 1972). In many circumstances, fibrosis progresses following cessation of exposure. The prevalence of abnormal X-rays is much less in groups exposed to lesser quantities of asbestos, such as shipyard or construction workers or workers exposed recently. Berry et al. (1979) have analyzed the development of clinical and x-ray signs of asbestosis according to accumulated exposure among workers of the Rochdale factory studied by Doll and Peto and others (see Section 3.9.3). The results suggest that the risk of developing possible asbestosis is less than 1 percent from an exposure to 0.7 f/ml for forty years. However, these results must be interpreted cautiously because all individuals studied began work with asbestos after 1950. The possibility of an increasing prevalence of abnormalities with progression of time, even with no further exposure, must be considered.

The British Occupational Hygiene Society (1983) evaluated the clinical, physiological, and X-ray findings among groups of workers exposed in two factories in Great Britain. From an analysis of the data they conclude that the probability of developing any one of seven pulmonary or radiographic abnormalities associated with asbestos exposure is less than 2 percent at cumulative exposures of 25 f-y/ml. As with Berry's analysis, the progression of abnormalities with time must be considered. Findings of abnormal X-rays, predominantly of the pleura, among family contacts of asbestos workers (Anderson and Selikoff, 1979) suggest that radiographic stigmata of asbestos exposure may occur at very low exposures if a long enough time elapses between

the exposure and the observation. The significance of pleural X-ray abnormalities is uncertain. They may or may not be associated with deficits in pulmonary function, and no information exists on whether the presence of pleural plaques or pleural thickening implies a greater risk of cancer separate from that associated with cumulative asbestos exposure.

Liddell and McDonald (1980) have correlated cause-specific mortality, 1951-1975, with the readings of the last available employment X-ray of a group of Canadian miners and millers. They found that significantly increased risks of death from pneumoconiosis, pulmonary TB, lung cancer, "other" respiratory disease, and diseases of the heart were associated with a previous abnormal X-ray. However, increased lung cancer risks were also found among individuals with no detected parenchymal fibrosis, but who may have had pleural abnormalities. Again, unknown progression of fibrosis could have occurred between the last reading and death.

In addition to disease and disablement during life, asbestosis has accounted for a large proportion of deaths among workers in some occupational groups. The first reports of the disease (Auribault, 1906; Murray, 1907) described complete eradication of workers in textile carding rooms. Much improvement in dust control has taken place in the industry since the turn of the century, but even recently those exposed to extremely dusty environments, such as textile mills, may have as much as 40 percent of their deaths attributable to this cause (Nicholson, 1976a). Groups with lesser exposures for 20 or more years, such as in mining and milling (Nicholson, 1976b) or insulation work (Selikoff et al., 1979) may have 5 to 20 percent of their deaths attributed to pneumoconiosis. All varieties of asbestos appear equally capable of producing asbestosis (Irwig et al., 1979). In groups exposed at lower concentrations, such as the families of workers, death from asbestosis has not been reported.

It is not clear what the dose-response relationship is for the most minimal manifestations of asbestos exposure, such as a pleural or diaphragmatic plaque or unilateral pleural thickening. The possibility exists that such abnormalities may develop in some individuals long after exposure to very low doses of asbestos (1-10 f-y/ml, for example.) This is suggested by the finding of significant percentages of such abnormalities among family contacts of asbestos workers. However, these x-ray abnormalities are unlikely to be associated with any discernible pulmonary function deficit in individuals exposed to less than 10 f-y/ml. At such exposures, the primary risk consideration is cancer rather than non-malignant disease.

3.14 MANIFESTATIONS OF OTHER OCCUPATIONAL EXPOSURES TO ASBESTOS

In the past decade, considerable evidence was developed on the prevalence of asbestos disease in workers exposed to a variety of work activities. Workers in shipyard trades (other than insulation work), in particular, were shown to have had significant exposure. By 1975, Harries (1976) identified 55 mesotheliomas in the Devonport Dockyard, only two of which were in asbestos workers. In a case-control study of four Atlantic Coast areas, an average relative risk for lung cancer of 1.4 was determined (Blot et al., 1978). The study population had an average employment time of only three years and no exposure data are available. X-ray abnormalities among non-insulator shipyard employees are also common. Among long-term (mostly 30+ year) shipyard workers, 86 percent have X-ray abnormalities characteristic of asbestos exposure (Selikoff et al., 1980). Maintenance personnel are also at risk from asbestos disease. Lillis et al. (1979) reported finding X-ray abnormalities among 55 percent of 20+ year chemical plant workers.

These findings are important because they point to sources of environmental asbestos emissions in the future. Removal of asbestos from friable products, including insulation material, and installation of engineering controls in factories have significantly reduced exposure and emissions from primary manufacturing or new construction work. However, more than one million tons of asbestos are in place as friable materials in ships, buildings, power plants, chemical plants, refineries, and other locations of high temperature equipment (Nicholson, 1976a). Maintenance, repair, and removal of this material will continue to be an important source of future exposure to workers and of emissions into the environment (both inside and outside buildings).

3.15 DEPOSITION AND CLEARANCE

Considerable data are available on the quantity of asbestos fibers in lungs of individuals with and without known exposures to asbestos (Sebastien et al., 1979; Jones et al., 1980; Wagner et al., 1982). Most of the cases analyzed were selected because of death from mesothelioma, often coupled with an investigation of a specific work group (Wagner et al., 1982; Berry and Newhouse, 1983). However, they have not been correlated with known cumulative exposures. Generally, amphibole burdens of heavily exposed individuals range from 10^7 to 10^8 fibers/gram dry weight; general population controls (in Great

Britain) are usually less than 10^6 fibers/gram dry weight (Jones et al., 1980). Similar concentrations of chrysotile are seen in exposed workers (Wagner et al., 1982) and unexposed controls (Jones et al., 1980).

Very few data are available that provide a basis for establishing a model for the deposition and clearance of fibers in humans. It is expected that both short- and long-term clearance mechanisms exist in humans, as in animals (see Chapter 4). If only long-term processes are considered (characterized by months or years) the simplest model is one in which the change in lung burden (N) is proportional to the rate of deposition of fibers (A) (assuming continuous exposure) diminished by a clearance that is proportional (by factor β) to the number of fibers present.

$$\frac{dN}{dt} = A - \beta N \quad (3-7a)$$

This yields for the number of fibers present after a constant exposure of duration, t_1 ,

$$N = \frac{A}{\beta}(1 - e^{-\beta t_1}) \quad (3-7b)$$

and at a time, t_2 after cessation of a constant exposure of duration t_1

$$N = \frac{A}{\beta}(1 - e^{-\beta t_1})e^{-\beta t_2} \quad (3-7c)$$

Such a model is applicable at times t_1 and t_2 which are long compared to any short-term clearance mechanisms. It is clearly a very simplistic model in that it considers only one characteristic time for long-term removal processes. Nevertheless, it illustrates the difficulty of applying even the simplest model. In order to systematize lung burdens, information is needed on the duration and intensity of the exposure and the time from last exposure in order to obtain a measure of the characteristic removal time for a given fiber type. Such information is not yet available for the individuals whose lungs have been analyzed.

Data have been presented by Bignon et al. (1978) on the number of amphibole fibers detected in lung washings of seven asbestos insulation workers. All were exposed between 10 and 16 years. While individual exposures are

unknown, fewer fibers were found in the washings of those longest removed from exposure. The data are consistent with a decrease of 50 percent in the number of washable fibers at five to seven years after cessation of exposure. However, it is noted that washable fibers may not be proportional to the residual lung burden or to the number of fibers trapped within lung tissue. The lung washings were largely amphibole; no corresponding data are available for chrysotile fibers.

Data on the fiber dimensions from these studies show a decrease in the average length and diameter of fibers found in the pleura compared with those found in the parenchyma. However, no distinction was made between amphiboles and chrysotile in this analysis, and the different length-width data could simply be a reflection of the predominance of chrysotile in the pleura.

3.15.1 Models of Deposition and Clearance

The Task Group on Lung Dynamics of the International Commission on Radiological Protection proposed a model for the deposition and retention of particles (see Brain and Valberg, 1974). The results of this model are shown in Figure 3-12, which depicts the percentages of particles of different sizes deposited in the various compartments of the respiratory tract. Figure 3-12 shows that alveolar deposition is dominant for particles with a mass median diameter less than $0.1\text{ }\mu\text{m}$. As the particle size increases, deposition in this area decreases, falling to 25 percent at $1\text{ }\mu\text{m}$ and to 0 at $10\text{ }\mu\text{m}$ or above. Nasal and pharyngeal surface deposition becomes important above $1\text{ }\mu\text{m}$ and rises rapidly to be the dominant deposition site for particles $10\text{ }\mu\text{m}$ in diameter or greater. This model was developed for spherical particles. Timbrell (1965) has shown that the settling velocities of particles, and their aerodynamics, are such that fibers with aspect ratios greater than three behave like particles with a diameter three times as great, independent of the length of the fiber. This was corroborated by calculations of Harris and Fraser (1976). Thus, few fibers with diameters as large as $2\text{ }\mu\text{m}$ are likely to penetrate into the alveolar spaces, although finer fibers, even as long as $200\text{ }\mu\text{m}$, may do so.

3.16 EFFECTS OF INTERMITTENT VERSUS CONTINUOUS EXPOSURES

Two distinct kinds of exposure occurred to workers in the different studies reviewed. In some production operations (e.g., textiles), workers are

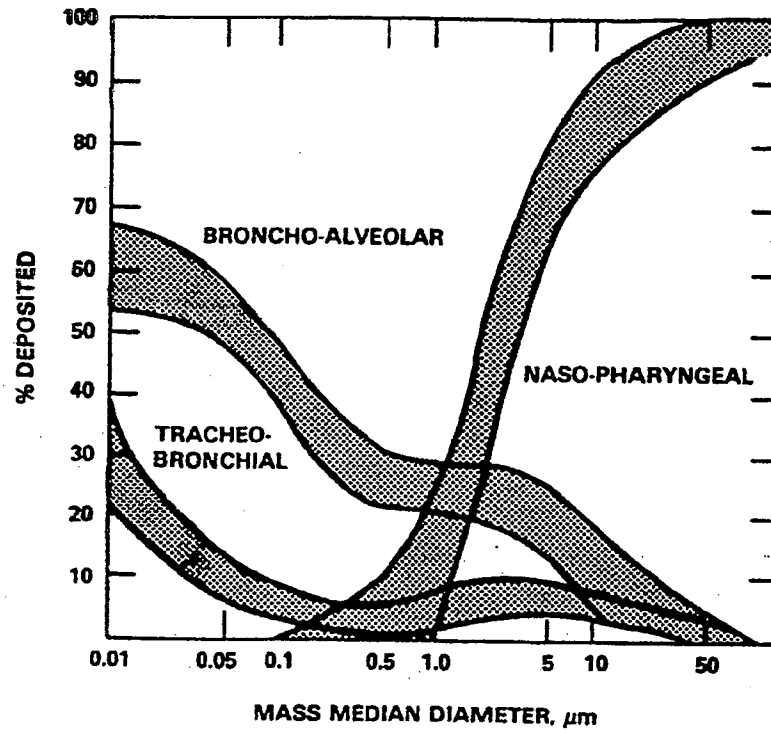


Figure 3-12. Aerosol deposition in the respiratory tract. Tidal volume is 1,450 ml; frequency, 15 breaths per minute. Variability introduced by change of sigma, geometric standard deviation, from 1.2 to 4.5. Particle size equals diameter of mass median size.

Source: Brain and Valberg (1974).

exposed to a relatively constant concentration of asbestos fiber throughout their work day; in other production operations (e.g., insulation, maintenance, and some production); workers are exposed to extremely variable concentrations of asbestos, with most of their cumulative exposure resulting from short duration, but intense, exposures. Implicit in the use of a linear dose-response relationship and average exposures is the concept that the risk of cancer is directly related to the cumulative asbestos exposure received in a period of time, i.e., the effect of an exposure to 100 f/ml for 1 hour is the same as that of 1 f/ml for 100 hours. (This equivalence applies only for short time periods. Because of the time dependence of mesothelioma risk, 100 f/ml for one year is not equivalent to 2 f/ml for 50 years.) Short, intense exposures could have an effect different from longer and lower exposures if clearance mechanisms are altered by very high concentrations of inspired asbestos. Although there are no data that directly address this question, indirect information suggests that the magnitude of the effect is less than the variability between studies with continuous exposure. Henderson and Enterline (1979) found that the excess lung cancer risk for plant-wide maintenance mechanics was only slightly higher (21 percent) than that for production workers, on a unit exposure basis. Curiously, the risk of pneumoconiosis was much less per unit of cumulative exposure among maintenance workers. The similarity of unit exposure risks of insulation workers compared to groups having continuous exposure suggests that the character of their exposure is not important. However, both comparisons depend upon the exposure estimates of the groups in question. Clearly, average exposures are difficult to estimate from episodic exposures and the above numerical similarities may be fortuitous. The unusually low pneumoconiosis risk among mechanics in the Henderson and Enterline (1979) study may be the result of exposure misestimates.

3.17 RELATIVE CARCINOGENICITY OF DIFFERENT ASBESTOS VARIETIES

Whether there is a different carcinogenic response according to fiber type or industrial process is an issue of increasing concern in the understanding of asbestos disease. Considerable controversy has developed as to whether one variety of asbestos (crocidolite) or mineral class (amphibole) is more carcinogenic than another (the serpentine mineral, chrysotile). Great

Britain, Canada, and Sweden have imposed far more rigid standards for crocidolite than other varieties of asbestos. In contrast, the United States has no special standard for any specific asbestos mineral.

Prior to the late 1960s the question was moot, because most epidemiological studies did not accurately characterize the asbestos fiber types used and measurements were not made of fiber concentration by mineral species. Most measurements only characterized the total quantity of dust in the aerosol (in terms of millions of particles per cubic foot) rather than in terms of fiber concentration. This lack of information on fiber exposure by mineral type was recognized at the time of the 1964 New York Academy of Sciences Conference on Asbestos (Whipple and van Reyen, 1965), and a recommendation was made that the importance of fiber type on the risk of developing asbestosis, carcinoma of the lung, and mesothelial tumors be investigated. In the ensuing years, considerable information was developed on the mortality experience of different groups exposed to different varieties of asbestos in different work processes. Unfortunately, the differential unit exposure risk associated with different fiber types is still not completely understood.

3.17.1 Lung Cancer

3.17.1.1 Occupational Studies. Figure 3-7, Table 3-28 and Table 3-10 summarize the information available on the unit exposure risk for lung cancer in 14 different epidemiological studies. The range of the fractional increase in lung cancer per unit asbestos exposure, expressed in terms of $f\text{-y/ml}$, varies by more than two orders of magnitude. What is unique about this variation is that exposures to a single fiber type yield results that differ by nearly 100-fold. One of the highest unit exposure risks was found in a textile plant that used only chrysotile asbestos (Dement et al., 1983b; McDonald et al., 1983a) and the lowest values were found in a large study of chrysotile mine and mill employees (McDonald et al., 1980) and in groups exposed only to chrysotile asbestos in friction products manufacturing (Berry and Newhouse, 1983; McDonald et al., 1984). Similarly, large (10-fold) differences are found in studies ostensibly of the same process, using the same mix and quality of asbestos fibers in different plants of the same company. A study of asbestos cement manufacturing shows one of the highest unit exposure risks (Finkelstein, 1983). Another study (Weill et al., 1979) suggests a risk more than 1/10 as much, while a 10-fold difference in risk appears to exist in two groups working at different periods in a single British Textile facility (Peto, 1980).

There is only one study in which the exposure was solely to amosite asbestos (Seidman, 1984), and the risk was comparable to the risk found in chrysotile textile operations. However, in several groups exposed to a mixture of chrysotile, amosite, and crocidolite in insulation work (Selikoff et al., 1979), the risk was less than that experienced by either chrysotile textile manufacturers or amosite factory workers.

No data exist, in any study, of unit exposure risks to workers exposed solely to crocidolite asbestos. Enterline and Henderson (1973) and Weill et al. (1979) suggest that workers exposed to chrysotile and crocidolite may have a greater lung cancer risk than those exposed to chrysotile alone, perhaps by a factor of two. However, this suggestion is based on air concentrations of total particles in the respective work environments (including much other dust) and a significant amount of crocidolite could also have been present without affecting the total particle count.

The wide divergence of risks according to fiber type, and even among similar work processes, suggests that factors other than mineral type substantially influenced the studies reviewed. These other factors could include errors in the estimation of exposures that occurred decades previously, biases or other limitations in epidemiological studies describing the disease experience, and statistical uncertainties associated with a limited number of deaths.

While the above factors undoubtedly contribute to some of the observed variability in Figure 3-7, certain consistent differences are likely to be real. Chrysotile textile production imparts a significantly higher risk per fiber exposure than chrysotile mining or friction products manufacturing. The data supporting this suggestion are very convincing for mining versus textiles. They are less convincing for friction products versus textiles because of greater uncertainties in the mortality experience of friction product workers and estimates of their fiber exposure.

McDonald et al. (1984) and others suggested that differences in risk may be caused by differences in fiber size and dynamics of penetration. As chrysotile is processed, the percentage of long curly fibers (which are easily counted but not easily inspired) decreases and the percentage of shorter, straighter, and narrower fibers increases.

3.17.1.2 Environmental Exposures. Data on the risk of lung cancer by fiber type from non-occupational exposures to asbestos are extremely scarce. Siemiatycki (1982) reported on the mortality experience of the general population of Asbestos and Thetford Mines, Quebec. These two areas account for the

great preponderance of chrysotile mining in Canada. The female population in these towns has experienced substantial exposure compared to that of individuals in non-mining areas. Data from Gibbs et al. (1980) indicate that recent town air concentrations range from 170 to 3500 ng/m². Additionally, home exposures to the wives of workers in the plant also occurred. Table 3-34 lists the mortality experience for selected causes among the female population of Asbestos and Thetford Mines during the years 1966-1977. The observed mortality was compared to the mortality experience of the entire Province of Quebec. There is no statistically significant excess of lung cancer among the mining population females compared to that expected. However, the use of the entire Province of Quebec as the reference population appears to be inappropriate, although the degree of inappropriateness is difficult to ascertain. Lung cancer rates in rural areas are considerably lower than those of urban centers. McDonald et al. (1971) stated that the lung cancer rate for males in the counties surrounding the mining area is two-thirds that of the Province as a whole. Table 3-20 gives the regional lung cancer incidence rates in Quebec Province for males and females for the years 1969-1973. The rate for males in rural counties is 73 percent of the rate in the Province, in agreement with McDonald et al. (1971); however, the relative rates for rural females is even lower, 62 percent of the Provincial rate. Thus, a female lung cancer relative risk of 1.06 compared to Quebec Province translates into a 70 percent increase compared to all of Quebec except Montreal and Quebec City.

TABLE 3-34. MORTALITY FROM SELECTED CAUSES IN ASBESTOS AND THETFORD MINES COMPARED TO QUEBEC PROVINCE, FEMALES, 1966-77.

Cause	O	E	O-E	L.C.L. ^a	O/E	U.C.L. ^a
All causes	1130	1274.6	-144.6	0.84	0.89	0.94
All cancers	289	318.1	-29.1	0.81	0.91	1.02
Digestive cancer	117	110.7	6.3	0.88	1.06	1.28
Respiratory cancer	23	21.5	1.5	0.68	1.07	1.61
Other respiratory diseases	30	51.8	-21.8	0.39	0.58	0.83

^a95 percent confidence limits.

Source: Siemiatycki (1982).

This increase is also compatible with data published by Wigle (1977) on cancer mortality in relation to asbestos in municipal water supplies. He compared the cancer risk, by site, for Asbestos and Thetford Mines with nearby communities having moderate concentrations of asbestos in their water supply, and with various other communities throughout the Province of Quebec, including some in populated and industrial areas. The relative cancer risk for females was 1.3 for Asbestos and Thetford Mines, 0.7 for five nearby towns, and 0.8 for other communities (some urban or industrial).

The increases indicated by the adjusted relative risks in Siemiatycki's (1982) study and those indicated by Wigle's (1977) data are both statistically significant. However, these data are only indicative and do not demonstrate an increased lung cancer risk due to environmental asbestos exposure, because the effect of confounding variables was not explored. Nevertheless, the data show that population comparisons between residents of Asbestos and Thetford Mines and other regions of Quebec cannot be used to indicate the absence of a risk.

3.17.2 Mesothelioma

3.17.2.1 Occupational Exposures. Table 3-31 lists values characterizing the risk of death from mesothelioma and lung cancer per f-y/ml in four studies, along with cruder estimates of the mesothelioma risk compared to that of lung cancer in 14 studies. One noticeable feature among all studies is that the ratios of the unit exposure risks of mesothelioma and lung cancer are very similar, irrespective of the type of exposure experienced. Thus, it appears that the same factors affect the variability of mesothelioma risk as affect lung cancer risk, and that mesothelioma risk can be estimated from values of K_L and an average ratio of K_M/K_L . Again, it appears impossible to separate the effect of mineral type from other factors contributing to the variability of potency.

In order to make a broader comparison of mesothelioma according to exposure by mineral type, the risk of pleural and peritoneal mesothelioma can be compared with that of lung cancer in a variety of studies. Because the asbestos risk of lung cancer is directly proportional to the underlying risk of lung cancer, the comparisons are most appropriately made to a lung cancer risk that is standardized to a similar background. In particular, one would expect the ratio of mesothelioma to excess lung cancer among women to be several

TABLE 3-35. RISK OF DEATH FROM MESOTHELIOMA AS A PERCENTAGE OF EXCESS LUNG CANCER, ACCORDING TO FIBER EXPOSURE

Study and fiber type	Obs. 0	Exp. E	Lung Cancer 0-E	Adj.	Mesothelioma		Mesothelioma as a % of excess of lung cancer	
					P1.	Tot.	P1./0-E	Tot./0-E
<u>Chrysotile</u>								
Acheson et al. (1982)	6	4.5	1.5	5.5	1	0	18.2	0.0
Dement et al. (1983a,b) ^a	33	9.8	23.2	18.5	0	1	0.0	18.2
McDonald et al. (1983a)	59	29.6	29.4	15.4	0	1	0.0	5.4
McDonald et al. (1980)	230	184.0	46.0	126.2 (166) ^a	10(20+) ^a	0	7.9(12.0+)	6.5
Nicholson et al. (1979) ^a	25	11.1	13.9	17.2	1	0	5.8	7.9(12.0+)
McDonald et al. (1984)	73	49.1	23.9	24.8 (0.0) ^b	0(3) ^b	0	0.0(very high)	5.8
Rubino et al. (1979)	9	8.7	0.3	0.3	1	0	333.3	0.0
Weiss (1977)	4	4.3	-0.3	-0.3	0	0	0.0	333.3
Totals (excluding ^a studies)				147.1	12	1	8.2	0.7
Totals (adj. for additional cases)				187	25	1	13.4 ^a	0.5
<u>Predominantly chrysotile (>90%)</u>								
McDonald et al. (1983b)	53	50.5	2.5	18.0	10	4	55.6	22.2
Robinson et al. (1979)	49	36.1	12.9	28.4	4	5	14.1	17.6
Robinson et al. (1979)	14	1.7	12.3	123.0	1	1	5.0	45.8
Mancuso & El-attar (1967)	33	14.8	18.2	28.3	1	8	35.3	5.0
Peto (1980)	30	15.5	14.5	12.0	7	0	58.3	26.3
Thomas et al. (1982)	22	25.8	-3.8	-3.8	2	0	--	0.0
Totals (some unknown duplications of deaths)				102.9	25	18	24.3	--
<u>Amosite</u>								
Acheson et al. (1984)	57	29.1	27.9	25.4	4	1	15.7	3.9
Seldman et al. (1979)	83	21.9	61.1	61.1	7	7	11.5	11.5
Totals				86.5	11	8	12.7	9.2
<u>Predominantly crocidolite</u>								
Acheson et al. (1982)	13	5.6	6.4	24.0	3	2	12.5	6.3
Hobbs et al. (1980)	60	38.2	21.8	21.8	17	0	78.0	0.0
Jones et al. (1980)	12	6.3	5.7	21.0	13	4	61.9	19.0
Mignall & Fox (1982)	10	3.7	6.3	23.2	9	3	38.8	12.9
McDonald & McDonald (1978)	7	2.4	4.6	16.8	3	6	17.9	35.7
Totals					45	13	42.1	12.2
		1	106.8			68		63.7

TABLE 3-35. (continued)

Study and fiber type	Obs. O	Exp. E	Lung Cancer O-E	Adj.	Mesothelioma Per.	Mesothelioma Tot.	Pl./O-E	Mesothelioma as a % of excess of lung cancer Per./O-E	Tot./O-E
Anthophyllite									
Meurman et al. (1974)	21	12.6	8.4	13.4	0	0	0.0	0.0	0.0
Totals				13.4	0	0	0.0	0.0	0.0
Talc (Tremolite)									
Kleinfield et al. (1974)	13	4.5	8.5	16.1	0	1	0.0	6.2	6.2
Brown et al. (1979)	9	3.3	5.7	8.6	0	0	0.0	0.0	11.6
Totals				24.7	0	1	0.0	4.0	8.1
Mixed exposures									
Albin et al. (1984)	12	6.6	5.4	12.2	4	0	32.8	0.0	32.8
Berry & Newhouse (1983) (M)	143	139.5	3.5	3.5	8	0	514.3	0.0	514.3
Berry & Newhouse (1983) (F)	6	11.3	-5.3	-5.3	2	0	--	--	--
Clemmesen & Hjalgrim-Jensen (1981)	47	27.3	19.7	26.2	3	0	11.5	0.0	11.5
Elmes & Simpson (1977)	27	5.0	22.0	59.4	8(19) ^d	5	32.0	8.4	40.4
Finkelstein (1983)	20	3.1	16.7	15.9	6	5	37.7	31.4	69.2
Henderson & Enterline (1979)	63	23.3	39.7	59.6	5	0	8.6	44.1	8.4
Selikoff et al. (1979) (US)	398	93.7	296.3	259	61	109	170	42.1	65.6
Selikoff et al. (1979) (NY-NJ)	93	13.1	79.9	106	11	27	38	25.5	35.8
Kleinfield et al. (1987)	10	1.4	8.6	14.4	1	2	6.9	13.9	20.8
Kolonel et al. (1980)	13	7.5	5.5	7.3	10	0	0.0	39.1	0.0
Newhouse & Berry (1979) (M)	103	43.2	59.8	69.1	19	27	27.5	39.1	66.6
Newhouse & Berry (1979) (F)	27	3.2	23.8	100	13	8	13.0	8.0	21.0
Nicholson (1976a)	27	8.4	18.6	22.6	8	7	35.4	0.0	66.4
Pantoni et al. (1979)	123	54.9	68.1	79.1	0	0	0.0	0.0	0.0
Rosiller & Coles (1980) ^a	84	100.3	-16.3	-16.3	--	--	--	--	--
Wells (1984)	188	128.0	60.0	79.5	8	1	7.5	5.3	13.8
Totals (except ^a study)				892.2	168	191	18.8	21.4	40.2

^aOne mesothelioma death is included in a larger study of McDonald et al. (1980).

^bSubsequent to termination of the study, many additional cases of mesothelioma developed. Four occurred in 1976 and 1977 (McDonald and Liddell, 1979) and six were found in one mining area in 90 consecutive autopsies during 1981-83. (Churg et al., 1984). To account for some of this increase, the additional 10 mesothelioma cases were included and the adjusted excess lung cancer deaths increased by 40 to account for mortality over the 5 additional years. The effect of considering these additional cases is illustrated by data in parentheses.

^cNo mesothelioma cases were found in the cohort. However, three deaths from mesothelioma were identified in the Connecticut Tumor Registry from the plant (Ieta et al., 1983). These are included in parentheses for the purposes of this analysis. While a high lung cancer risk was noted in the cohort, the absence of a dose-response relationship made attribution of the cause difficult and no lung cancer deaths were attributed to asbestos exposure.

^dThe adjusted excess lung cancer risk is unrealistically high. A value of 20 will be used.

^eEleven deaths were either from pleural mesothelioma or lung cancer. In this analysis, all were considered mesothelioma.

^fBest estimate data on the cause of death.

times higher than among men because of the greater background risk of lung cancer among men. Table 3-35 lists the various studies from Table 3-2. In each study, an attempt was made to estimate an excess lung cancer risk that would have occurred if the U.S. male rates in 1970 had prevailed for the study population. For example, the standardized number of deaths in women was calculated by multiplying the number of observed deaths minus the expected number of deaths by the ratio of the age standardized male to female lung cancer rate. Similar adjustments were made to the excess number of lung cancers of cohorts followed for long periods of time, that would have had an average time of death earlier than 1970. Adjustments were also made where the lung cancer rates of other nations differed from those in the United States. The last two adjustments led to only minor changes in most cohorts, while the adjustment for gender was substantial and uncertain because of absence of information about the smoking habits of the study group. Finally, adjustments to local rates were made similar to those in Section 3.9. After all the adjustments were made, the ratio of mesothelioma was calculated by type of fiber exposure as a percentage of adjusted excess lung cancer. The results were summed and the combined data for specific mineral exposures were obtained.

There are several limitations to consider when reviewing these data. Because of possible bias caused by underdiagnosis of peritoneal mesothelioma in many cohorts, the principal focus should be on the ratios of pleural mesothelioma to adjusted excess lung cancer. Tissue specimens of all abdominal tumors were reviewed in only a few studies (Selikoff et al., 1979; Seidman, 1984; Newhouse and Berry, 1979; Finkelstein, 1983) to determine if peritoneal mesothelioma had been misdiagnosed. Because of the ongoing review of mesotheliomas in Canada by the McDonalds (McDonald and McDonald, 1978; McDonald et al., 1970, 1971), the study of Canadian miners and gas mask workers can also be considered to have benefited from review. These studies account for 194 of 236 identified peritoneal mesotheliomas. Substantial bias may also exist because of studies in which the tracing of the cohort is limited; in some studies as many as 39 percent of the exposed individuals were untraced. The inadequacy of tracing was particularly high in studies of workers exposed to crocidolite. The danger is that mesotheliomas were identified in registries because of their uniqueness, but that lung cancers in untraced individuals were not. Thus, it is likely that there is a substantial overestimate of the number of mesotheliomas relative to lung cancer associated with crocidolite

exposures. Also, the comparison of the ratio of mesothelioma to excess lung cancer is uncertain because of substantially different time courses for the two diseases. The time course for lung cancer is determined by the time course of the underlying risk, which is usually the time course of lung cancer from cigarette smoking. On the other hand, the time course for mesothelioma is strictly dependent upon the time from onset of exposure, rising at about the fourth or fifth power of time from first exposure. The analysis utilized in Table 3-35 does not fully account for such differences.

In comparing the different ratios of pleural mesothelioma to adjusted lung cancer for all studies in which the major exposure was to one fiber type, the ratios for chrysotile, amosite, and mixed exposures are roughly comparable. Crocidolite exposures have a twofold to threefold greater number of pleural mesotheliomas relative to excess adjusted lung cancer. However, as noted previously, the untraced individuals in the various crocidolite cohorts may have led to an overestimate of this ratio. The possibility of underdiagnosis of mesothelioma notwithstanding, the risk of peritoneal mesothelioma is much lower with pure chrysotile exposures than with amphiboles or mixed exposure. Only one peritoneal mesothelioma has been identified among more than 25 mesotheliomas in chrysotile-exposed populations. Though a greater mesothelioma potency may be considered for crocidolite (a factor of two or four considering both pleural and peritoneal sites), the effect of other factors in a given exposure circumstance leads to much greater differences, as for example in the case of lung cancer, where different exposure circumstances with the same fiber lead to nearly 100-fold differences in unit exposure risk. A similar situation exists with mesothelioma where the manufacture of amosite insulation is associated with a high risk of mesothelioma (see Table 3-34), while amosite mining demonstrates little excess risk (Webster, 1978; Solomons, 1984). Also, great differences in risk appear to exist between the crocidolite mines of the Transvaal and those of the Cape Province. Thus, any suggestion that there are dramatic differences between asbestos varieties has to be considered in the light of greater differences that appear to be related to processing, fiber size distribution effects within a single asbestos variety (e.g., the difference between textiles and mining), and to differences between cohort studies of the same exposure circumstances (e.g., the asbestos cement studies of Weill et al. (1979) and of Finkelstein (1982, 1983), or the two cohorts of Peto (1980).

There was no evidence in Table 3-10 of a substantial difference in lung cancer unit exposure risk attributable to fiber type. While a pure amosite exposure had a unit exposure risk about twice that of chrysotile exposures, the combination of amosite or crocidolite with chrysotile in other exposure circumstances demonstrated lower unit exposure risks. The data from Tables 3-31 and 3-35 indicate the crocidolite mesothelioma to lung cancer risk ratio is no more than four times that of other fibers, and when crocidolite is used with other fibers, the combined ratio differs little from non-crocidolite exposures. These findings suggest that crocidolite or amphibole exposures cannot be the explanation of most mesotheliomas found in some predominantly chrysotile exposure circumstances (e.g., Canadian mining and milling and Rochdale, England textile production). This conclusion is further supported by the observation that all the mesotheliomas in the above circumstances were of the pleura, whereas amphibole exposure generally produces comparable numbers of pleural and peritoneal mesotheliomas (the study of Hobbs et al. (1980) is a remarkable exception). Finally, in the case of the Rochdale factory, the risk of mesothelioma in a factory using only 2.6 percent crocidolite from 1932-1968 (Doll and Peto, 1985) was as high as the risk in the London factory studied by Newhouse and Berry (1979) in which large amounts of crocidolite and amosite were used.

A careful consideration of the role of amphiboles in the production of mesothelioma is important for control of asbestos disease. On the one hand, it would be a mistake to minimize or ignore the mesothelioma risk of chrysotile. Millions of tons of this fiber presently are in building materials and other products. The potential for release in future years is substantial unless proper work practices and care are utilized during repair and maintenance work. On the other hand, it should be recognized that crocidolite, particularly, is a very dangerous asbestos material. This comes from two aspects of the fiber. One is the above-mentioned 2-4 fold greater risk of mesothelioma relative to lung cancer found in crocidolite exposure circumstances. This certainly indicates a greater unit exposure risk for mesothelioma relative to other asbestos fibers. Secondly, the large percentage of thin fibers in a crocidolite aerosol (which may contribute to increased risk mentioned above) also may contribute to a greater fiber exposure when crocidolite-containing products are manufactured or used because these very thin fibers remain aloft for longer periods of time. Considering all factors, the proscription on the

use of crocidolite in several countries would appear to be justified. Fortunately, few pure crocidolite exposure circumstances exist in the United States. Subject to their uncertainties, the average values of K_L and K_M reflect the most important processes where crocidolite is a constituent of the material being produced. Nevertheless, if a pure crocidolite exposure is encountered, a mesothelioma risk greater than that estimated using the average value of K_M is likely to exist and correspondingly greater precautions should be exercised.

3.17.2.2. Environmental Exposures. Mesothelioma has been documented in a variety of non-occupational circumstances, including family contacts of asbestos-exposed individuals. Table 3-36 lists observed family contact mesotheliomas associated with three occupational exposure circumstances and mesotheliomas identified in the contact worker group (the observation periods are not quite commensurate). It is important to note that family contact cases are seen with exposure to chrysotile, amosite and crocidolite. By fiber type, there appears to be little difference in the family contact risk relative to the risk at work.

TABLE 3-36. MESOTHELIOMA FROM FAMILY CONTACT
IN THREE OCCUPATIONAL CIRCUMSTANCES

Occupation	Country	Fiber type	Mesothelioma	
			Family members	Workers
Miners and millers	Canada	Chrysotile	3 ^a	12 ^b
Insulation manufacturers	U.S.A.	Amosite	4 ^c	14 ^d
Mixed products	U.K.	Mixed	9 ^e	67 ^f

^aMcDonald and McDonald (1980).

^bMcDonald et al. (1980).

^cAnderson (1976).

^dSeidman et al. (1979).

^eNewhouse and Thomson (1965).

^fNewhouse and Berry (1979).

Animal studies support this conclusion and suggest that all varieties of asbestos should be considered equally potent with respect to the production of either lung cancer or mesothelioma in both inhalation and implantation studies.

As discussed previously, many risk differences may be accounted for by differences in fiber size distributions in different work environments, rather than by fiber type. The greatest percentage of longer and thicker fibers

occurs in the work environment of miners and millers. Asbestos used in manufacturing processes is broken apart while it is incorporated into the finished product. During application or removal of insulation products it is further manipulated and the fibers become further reduced in length and diameter with many falling within the range of significant carcinogenic potency (see Section 4-6). Because these shorter and thinner fibers can readily be carried to the periphery of the lung where they penetrate the visceral pleura and lodge in the visceral or parietal pleura, they may be of importance in the etiology of mesothelioma. Bignon, Sebastien, and their colleagues (1978) reported data from a study of lungs and pleura of shipyard workers. Larger fibers, often amphibole, were found in lung tissue. In the pleura, the fibers were generally chrysotile, but shorter and thinner. The early association of mesothelioma with crocidolite occurred because, even in mining, crocidolite is readily broken apart, yielding many fibers in a respirable and carcinogenic size range, and has been extensively used in Great Britain in extremely dusty environments (e.g., spray insulation), creating high exposures for many individuals, with a concomitant high risk of death from mesothelioma. Thus the disease came to attention (Wagner et al., 1960). The mining and milling of chrysotile, on the other hand, involves exposures to long and curly fibers which are easily counted but not easily inspired.

Recent exposures in Turkey to the fibrous zeolite mineral, erionite, have been associated with mesothelioma. Results reported by Baris et al. (1979) demonstrate an extraordinary risk; annual incidence rates of nearly 1 percent exist for mesothelioma. In 1974, 11 of 18 deaths in Karain, Turkey were from this cause. The fiber lengths are highly variable; most erionite fibers are shorter than 5 μm and 75 percent are less than 0.25 μm .

3.18 SUMMARY

Data are available that allow unit risks to be determined for lung cancer and mesothelioma. The values for K_L , the fractional risk per f-y/ml, vary widely among the studies, largely because of the statistical variability associated with small numbers but also because of uncertainties associated with methodology and exposure estimates. Based on an analysis of the unit exposure risk for lung cancer and mesothelioma in 11 studies (all studies for which unit exposure risks can be estimated except chrysotile mining and milling),

the best estimate for K_L is 0.010, and for K_M it is 1.0×10^{-8} . An analysis of variability suggests that the 95 percent confidence limit on the estimate of K_L is generally from 0.0040 to 0.027 (a factor of 2.5), but for K_L in an unknown exposure circumstance it is a factor of 10. A greater range of uncertainty applies to the best estimate for the value of K_M , the uncertainty in a given exposure circumstance is also greater, perhaps by a factor of 20. Differences in asbestos type cannot explain the variability of K_L observed in different studies. However, the lower risk values found in chrysotile mining and milling compared with chrysotile textile production suggest that fiber length and width distribution is important. The unit exposure mesothelioma risk also differs greatly in different exposure circumstances, but the ratio of mesothelioma risk to excess lung cancer risk is relatively constant. Peritoneal mesothelioma has largely been associated with amphibole exposure, although this is qualified by the possibility of underdiagnosis in some studies. Pleural mesothelioma is associated with exposure to chrysotile and crocidolite; while differences in pleural mesothelioma risk attributable to fiber type may exist, they are much less than differences attributable to other factors.

4. EXPERIMENTAL STUDIES

4.1 INTRODUCTION

Most animal studies of asbestos health effects have been used to confirm and extend previously established human data rather than to predict human disease. This situation exists because asbestos usage predates the use of animal studies for ascertainment of risk; because some animal models are relatively resistant to the human diseases of concern; and because lung cancer, the principal carcinogenic risk from asbestos, is the result of a multifactorial interaction between causal agents, principally cigarette smoking and asbestos exposure, and is difficult to elicit in a single exposure circumstance. Although all of the asbestos-related malignancies were first identified in humans, experimental animal studies confirmed the identification of the diseases and provided important information, not available from human studies, on the deposition, clearance, and retention of fibers, as well as cellular changes at short times after exposure. Unfortunately, one of the most important questions raised by human studies, that of the role of fiber type and size, is only partially answered by animal research. Injection and implantation studies in animals have shown longer and thinner fibers to be more carcinogenic once in place at a potential site of cancer. However, the size dependence of the movement of fibers to mesothelial and other tissues is not fully elucidated, and the questions raised by human studies concerning the relative carcinogenicity of different asbestos varieties still remain.

4.2 FIBER DEPOSITION AND CLEARANCE

Deposition and clearance of fibers from the respiratory tract of rats were studied directly by Morgan and his colleagues (Morgan et al., 1975; Evans et al., 1973) using radioactive asbestos samples. Following 30-minute inhalation exposures in a nose breathing apparatus, deposition and clearance from the respiratory tract were followed. The distribution of fibers in various organ systems was determined at the conclusion of inhalation, showing that 31-68 percent of inspired fibrous material is deposited in the respiratory tract. The distribution of that deposited material is shown in Table 4-1. Rapid clearance, primarily from the upper respiratory tract (airways above the

TABLE 4-1. DISTRIBUTION OF FIBER AT THE TERMINATION OF 30-MINUTE INHALATION EXPOSURES IN RATS (PERCENT OF TOTAL DEPOSITED)

Fiber	Nasal passages ^a	Esophagus	Gastro-intestinal tract	Lower respiratory tract	Percent deposited ^b
Chrysotile A	9 ± 3	2 ± 1	51 ± 9	38 ± 8	31 ± 6
Chrysotile B	8 ± 2	2 ± 1	54 ± 5	36 ± 4	43 ± 14
Amosite	6 ± 1	2 ± 1	57 ± 4	35 ± 5	42 ± 14
Crocidolite	8 ± 3	2 ± 1	51 ± 9	39 ± 5	41 ± 11
Anthophyllite	7 ± 2	2 ± 1	61 ± 8	30 ± 8	64 ± 24
Fluor amphibole	3 ± 2	1 ± 1	67 ± 5	29 ± 4	68 ± 17

^aMean and standard deviation.^bPercent of total inspired.

Source: Morgan et al. (1975).

trachea), occurs within 30 minutes; up to two-thirds of the fibers are swallowed and found in the GI tract.

Clearance from the lower respiratory tract (trachea to alveoli) proceeds more slowly and two distinct components of clearance are observed. The first, believed to be caused by macrophage movement, leads to elimination of a considerable portion of the material deposited in the lower respiratory tract at a half life of 6-10 hours. The slower component that follows has a half-life of 60-80 days and involves clearance from the alveolar spaces. Data for a synthetic fluor amphibole (Figure 4-1) show one short-term and two long-term components for clearance of fibers. Other data on the lung content of animals, sacrificed at various times after exposure, show only a single long-term clearance component (Morgan et al., 1978); however, the ratio of fibers in the feces to those in the lung at the time of sacrifice is not a constant, as would be expected from a single exponential clearance mechanism.

By extrapolating curves like that of Figure 4-1 to zero-time for a variety of fibers, it is possible to ascertain the relative amounts of fibers

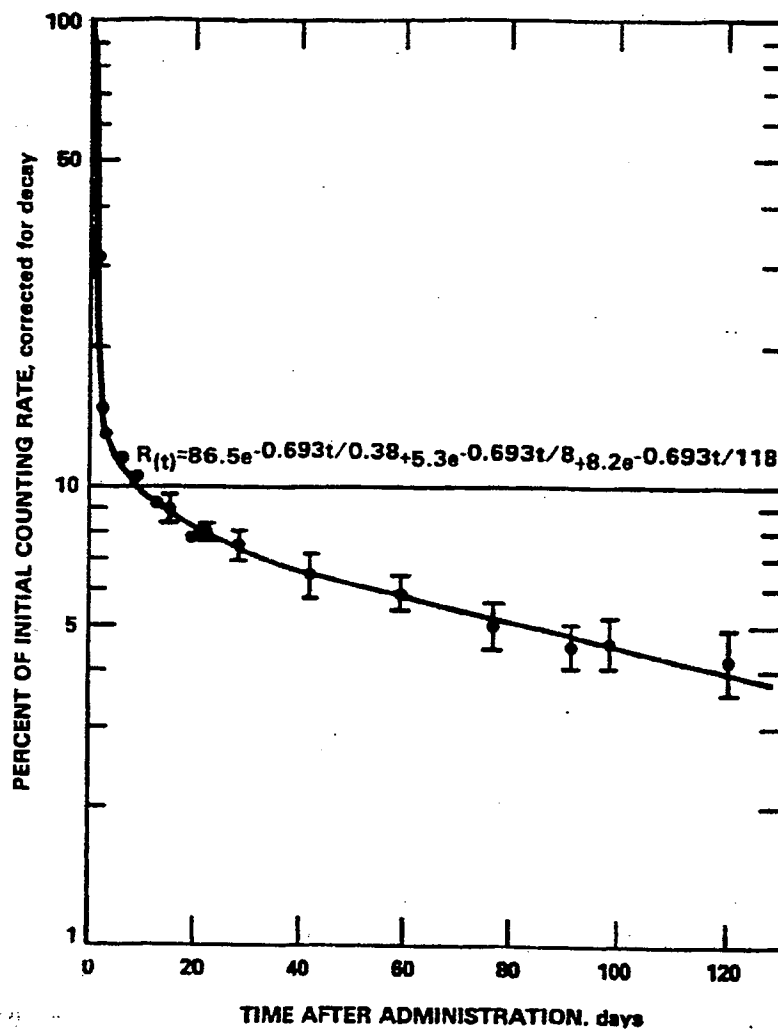


Figure 4-1. Measurements of animal radioactivity (corrected for decay) at various times after inhalation exposure to synthetic fluoramphibole. Mean result for three animals expressed as a percentage of the counting rate measured immediately after exposure.

Source: Morgan et al. (1977).

deposited in the bronchiolar-alveolar spaces. These data are shown for different fibers in Figure 4-2. The relative similarity of the percentage deposited in the lower bronchioles or alveoli for different fiber diameters is a reflection of two competing processes: at lower fiber diameters, the fibers can be inspired and then expired without impaction in the lower respiratory tract, but as the fiber diameter increases, impaction in the upper respiratory tract becomes important, leading to a lower percentage being carried to the alveolar spaces.

Morgan et al. (1978) also studied the length distribution of fibers that remain in the lungs of rats to determine the significance of fiber length on clearance. They found that the shorter fibers are preferentially removed within one week following inhalation and suggested that longer fibers reaching the alveolar spaces are trapped.

The radioactive chrysotile used in the clearance experiments allows autoradiography to demonstrate the location of fibers at different times after exposure. At 48 hours after exposure, the distribution of fibers in the lung is relatively uniform. However, at later times, there is a movement of fibers to the periphery of the lung where they accumulate in subpleural foci consisting of alveoli filled with fiber-containing cells.

Other data on the deposition and retention of inhaled asbestos were reported by Wagner et al. (1974). Figure 4-3 shows the dust content of rat lungs following exposures to different asbestos varieties. In the case of amphibole exposures, a linear increase in the amount of retained fiber was seen, whereas for chrysotile, the content of the lung rapidly reached an equilibrium between removal or dissolution processes and deposition, and did not increase thereafter. The long-term build-up of the amphiboles indicates that, in addition to the clearance processes observed by Morgan et al. (1977), there is a virtual permanent retention of some fibers. Using a minute volume for the rat of 100 ml, it would appear that about 1 percent of the total crocidolite or amosite inhaled is retained permanently in the lung.

The finding of a rapid movement from the upper respiratory tract and a slower clearance from the lower respiratory tract to the GI tract demonstrates a route of exposure that may be important for GI cancer. The observation in humans of peritoneal mesothelioma, of excess cancers of the stomach, colon, and rectum, and possibly of cancers at other non-respiratory sites, such as

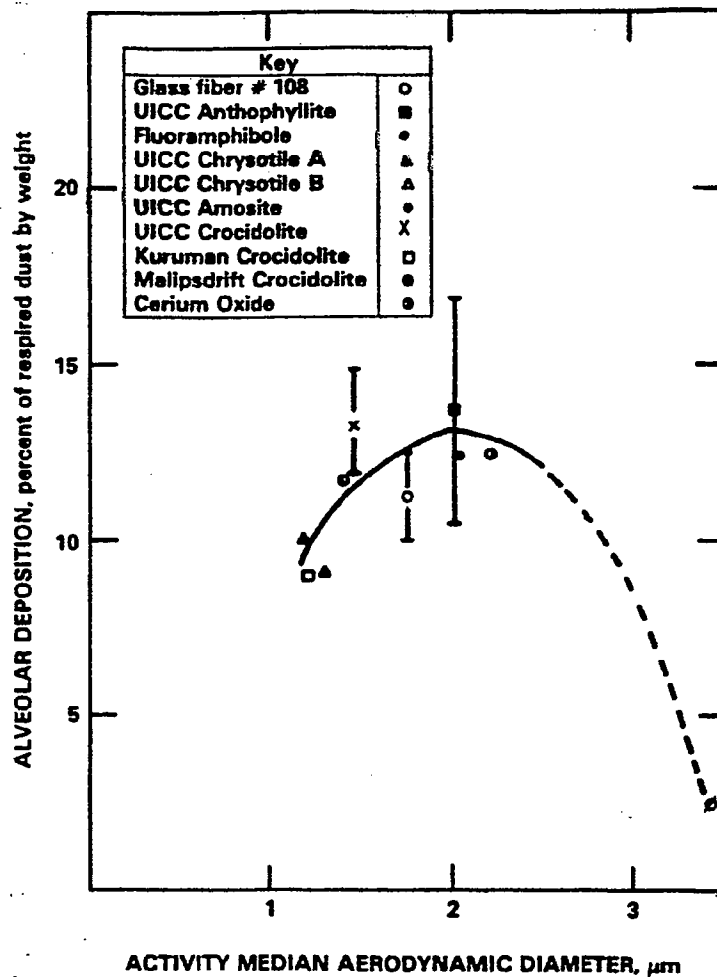


Figure 4-2. Correlation between the alveolar deposition of a range of fibrous and non-fibrous particles inhaled by the rat and the corresponding activity median aerodynamic diameters.
Source: Morgan (1979).

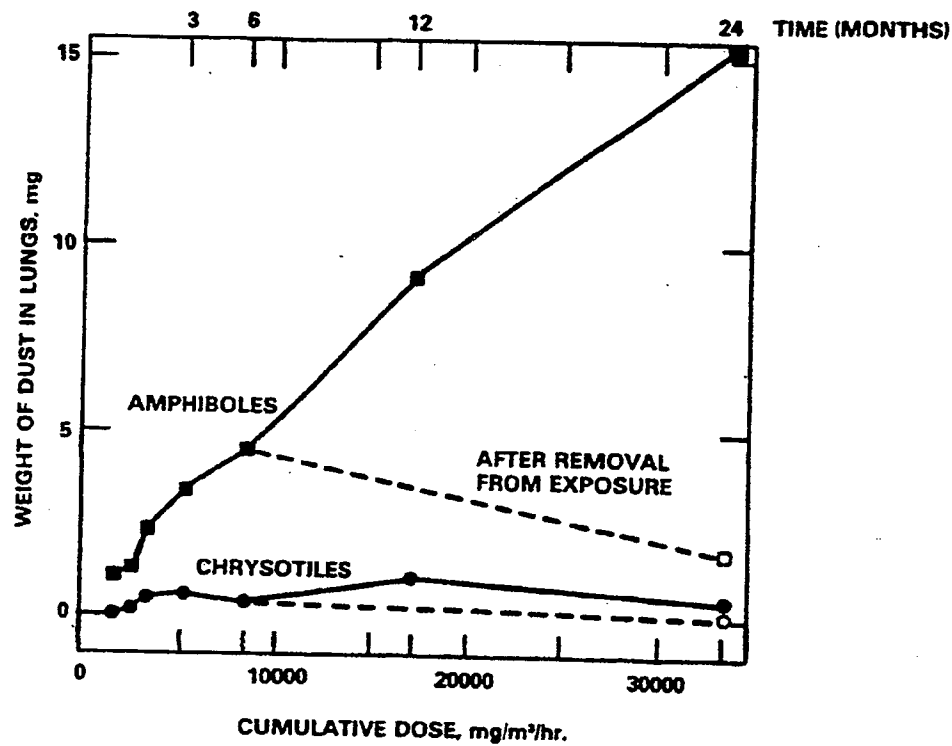


Figure 4-3. Mean weight of dust in lungs of rats in relation to dose and time.

Source: Wagner et al. (1974).

the kidney, could result from the migration of such fibers to and across the gastrointestinal mucosa. Additionally, fibers may reach organs in the peritoneal cavity by transdiaphragmatic migration or lymphatic-hematogenous transport.

4.3 CELLULAR ALTERATIONS

Several studies describe cellular changes in animals following exposure to asbestos. Holt et al. (1964) describe early (14-day) local inflammatory lesions found in the terminal bronchioles of rats following inhalation of asbestos fibers. These lesions consist of multi-nucleated giant cells, lymphocytes, and fibroblasts. Progressive fibrosis follows within a few weeks of the first exposure to dust. Davis et al. (1978) describe similar early lesions found in rats, consisting of a proliferation of macrophages and cell debris in the terminal bronchioles and alveoli.

Jacobs et al. (1978) fed rats 0.5 mg or 50 mg of chrysotile daily for 1 week or 14 months and subsequently examined GI tract tissue by light and electron microscopy. No effects were noted in the esophagus, stomach, or cecal tissue, but structural changes in the ileum were seen, particularly of the villi. Considerable cellular debris was detected in the ileum, colon, and rectal tissue by light microscopy. Electron microscopy data confirm the light microscopy data and indicate that the observed changes are consistent with a mineral-induced cytotoxicity.

A single oral administration of 5-100 mg/kg of chrysotile to rats produces a subsequent increase in thymidine in the stomach, duodenum, and jejunum (Amacher et al., 1975), suggesting that an immediate response of cellular proliferation and DNA synthesis may be stimulated by chrysotile ingestion.

4.4 MUTAGENICITY

Many studies showed asbestos not to be mutagenic, e.g., in Escherichia coli and Salmonella typhimurium tester strains (Chamberlain and Tarmy, 1977). Newman et al. (1980) reported that asbestos has no mutagenic ability in Syrian hamster embryo cells, but may increase cell permeability and allow other mutagens into the cell. Mossman et al. (1983) showed that UICC (Union Internationale Contra le Cancer) crocidolite and chrysotile do not produce DNA strand

breaks in the alkylane elution assay when applied to cultured hamster tracheal cells. Similar negative results were obtained by Lechner et al. (1983) with respect to induction of DNA strand breakage in human bronchial organ cultures treated with UICC chrysotile, amosite, and crocidolite. Finally, Hart et al. (1979) demonstrated that asbestos does not produce unscheduled DNA synthesis in human fibroblasts or single or double strand breaks.

However, a few studies do show mutagenicity. Sincock (1977) used several chrysotile, amosite, and crocidolite samples to show that an increased frequency of polyploids and cells with fragments results from passive inclusion of asbestos in the culture media of Chinese hamster ovary (CHO)-K1 cells. Similarly, Lavappa et al. (1975) showed that chrysotile induced a significant and exposure-related increase in chromosome aberrations in cultured Syrian hamster embryo cells. Amosite, chrysotile, and crocidolite were found to be weakly mutagenic in Chinese hamster lung cells in the 6-thioguanine-resistance assay (Huang, 1979). Livingston et al. (1980) showed that exposure to crocidolite and amosite can increase the sister chromatid exchange rate in Chinese hamster ovarian fibroblasts.

The evidence for chromosomal effects in human cells is contradictory. Valerio et al. (1980) found that freshly isolated lymphocytes undergo chromosomal changes when treated with UICC Rhodesian chrysotile. In contrast, Sincock et al. (1982) found negative effects with lymphocytes exposed to UICC crocidolite. Asbestos was shown to be highly cytotoxic in a variety of preparations (e.g., Mossman et al., 1983; Chamberlin and Brown, 1978).

In summary, while some evidence exists for aneuploidy caused by asbestos, most studies show that asbestos probably is not mutagenic in the classic sense of causing gene mutations and/or chromosomal breakage.

4.5 INHALATION STUDIES

The first unequivocal data that showed a relationship between asbestos inhalation and lung malignancy in laboratory animals were those of Gross et al. (1967) who observed carcinomas in rats exposed to a mean concentration of 86 mg/m³ chrysotile for 30 hours a week from the age of 6 weeks. Of 72 rats surviving for 16 months or longer, 19 developed adenocarcinomas, 4 developed squamous cell carcinomas, and 1 developed a mesothelioma. No malignant tumors were found in 39 control animals. A search was made for primaries at other

sites which could have metastasized and none were found. These and other data are summarized in Table 4-2.

Reeves et al. (1971) found two squamous cell carcinomas in 31 rats sacrificed after 2 years following exposure to about 48 mg/m^3 of crocidolite. No malignant tumors were reported in rabbits, guinea pigs, or hamsters, or in animals exposed to similar concentrations of chrysotile or amosite. No details of the pathological examinations were given.

In a later study (Reeves et al., 1974), malignant tumors developed in 5 to 14 percent of the rats that survived 18 months after exposure. Lung cancer and mesothelioma were produced by exposures to amosite and chrysotile, and lung cancer was produced by crocidolite inhalation. Again, significant experimental details were not provided; information on survival times and times of sacrifice would have been useful. Available details of the exposures and results are given in Table 4-3. While the relative carcinogenicity of the fiber types was similar, the fibrogenic potential of chrysotile, which had been substantially reduced in length and possibly altered by milling (Langer et al., 1978), was much less than that of the amphiboles. These results are also discussed in a later paper by Reeves (1976).

The most important series of animal inhalation studies is that of Wagner et al. (1974, 1977). Wagner exposed 849 Wistar SPF rats to the five UICC asbestos samples at concentrations from 10.1 to 14.7 mg/m^3 for times ranging from 1 day to 24 months. These concentrations are typically 10 times those measured in dusty asbestos workplaces during earlier decades. For all the exposure times, 50 adenocarcinomas, 40 squamous-cell carcinomas, and 11 mesotheliomas were produced. All varieties of asbestos produced mesothelioma and lung malignancies, in some cases from exposures as short as 1 day. Data from these experiments are presented in Tables 4-4 and 4-5. These tumors follow a reasonably good linear relationship for exposure times of 3 months or greater. However, the incidence in the 1-day exposure group is considerably greater than expected. Exposure had a limited effect on length of life. Average survival times varied from 669 to 857 days for exposed animals versus 754 to 803 days for controls. The development of asbestosis is also documented. There are 17 lung tumors, 6 in rats with no evidence of asbestosis and 11 in rats with minimal or slight asbestosis. Cancers at extrapulmonary sites are listed. Seven malignancies of ovaries and eight malignancies of male genitourinary organs were observed in the exposed groups of approximately 350 male